AUG 26 1932

VOLUME 50 NUMBER 2

ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

ARTHUR BLOOMFIELD, San Francisco
N. C. GILBERT, Chicago
REGINALD FITZ, Boston
J. H. MUSSER, New Orleans
RUSSELL M. WILDER, Rochester, Minn.

AUGUST, 1932

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized June 14, 1918.

CONTENTS OF PREVIOUS NUMBER

JULY, 1932. NUMBER 1

Diffuse Hemorrhage from the Stomach. Edward L. Bortz, M.D., Philadelphia.

Use of Liver Extract Intravenously: Report of Ten Cases. Paul J. Fouts, M.D., and L. G. Zerfas, M.D., Indianapolis.

Variations in the Total Blood Lipid in Alimentary Lipemia. H. F. Wechsler, M.D., New York.

Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes. T. L. Althausen, M.D., San Francisco, and E. Thoenes, Dr.med., Leipzig, Germany.

I. Fasting and Administration of Thyroxine.

II. Phosphorus Poisoning.

Solar Radiation in Relation to Endemic Goiter. James H. Smith, M.D., Richmond, Va.

Effects of Prolonged Liver Dietary in Pernicious Anemia: Case Reports of Three Patients Receiving Liver Therapy for Nine and a Half, Eight and Seven Years, Respectively. R. B. Gibson, Ph.D., and W. M. Fowler, M.D., Iowa City.

Myocardial Infarction or Gross Fibrosis: Analysis of One Hundred Necropsies. James R. Lisa, M.D., and Alfred Ring, M.D., New York.

Bismuth Diuresis and the Blood and Urinary Changes Under Clinical Conditions. A. B. Stockton, M.D., San Francisco.

Experimental Low Colonic Obstruction. George M. Roberts, M.D., and Lathan A. Crandall, Jr., M.D., Chicago.

Toxicity of Mersalyl (Salyrgan): A Clinical and Anatomic Study. Leonard Tarr, M.D., and Sheldon Jacobson, M.D., New York.

Book Reviews.

COPYRIGHT, 1932, BY THE AMERICAN MEDICAL ASSOCIATION

Archives of Internal Medicine

VOLUME 50 AUGUST, 1932 NUMBER 2

PERICARDITIS

I. CHRONIC ADHERENT PERICARDITIS

HARRY L. SMITH, M.D.

AND

FREDRICK A. WILLIUS, M.D.

ROCHESTER, MINN.

Adherent pericarditis is acknowledged to be one of the most difficult cardiac conditions to diagnose, and this statement is confirmed by analysis of records of necropsies. In relatively few cases is the condition positively identified while the patient is alive.

Numerous reasons exist for this inaccuracy of diagnosis. Foremost among them is the clinician's lack of suspicion regarding the possible existence of the disease. There may be complete absence of symptoms and signs, and this obviously renders identification of the disease impossible. The didactic overemphasis on so-called characteristic signs has gone far toward frustrating correct diagnosis, for in reality such signs exist in relatively few cases, and their absence often influences the clinician against committing himself. The occurrence of associated disease entirely unrelated to the cardiovascular system may so dominate the clinical picture that attention may be exclusively centered on the principal disease. Likewise, associated disease of the heart may apparently satisfactorily explain the patient's symptoms, and thought of additional pathologic change in the heart is summarily dismissed.

This investigation was undertaken with the foregoing facts clearly in mind, to determine, if possible, additional data and correlation that might be instrumental in more accurate diagnosis of a hitherto elusive disease.

MATERIAL

The records of necropsies of the Mayo Clinic were critically studied, and among the 8,912 cases, 373 cases of pericarditis were found, an incidence of 4.2 per cent. The incidence in this group is considerably smaller than in those previously studied and reported on. Wells,[1] in 1,048 cases examined post mortem, found pericarditis in 11.3 per cent; Locke,[2] in 3,683, demonstrated pericarditis in 16.6 per cent; Musser

From the Section on Cardiology, the Mayo Clinic.

1. Wells, H. G.: The Pathology of the Healed Fibrous Adhesions of the Pericardium, Am. J. M. Sc. **123**:241 (Feb.) 1902.

2. Locke, E. A.: The Occurrence and Diagnosis of Pericarditis, Boston M. & S. J. **175**:590 (Oct. 26) 1916.

and Herrmann,[3] in 1,720, found pericarditis in 17.7 per cent. In the 15,363 cases examined post mortem, just mentioned, pericarditis was found to occur in 1,406, an incidence of 9.2 per cent.

In the series from the Mayo Clinic, adherent pericarditis occurred in 144 (that is, in 38.4 per cent of the cases of pericarditis). These 144 cases form the basis for this study.

Sex and Age Incidence.—Males predominate in our series. There were one hundred males (69.4 per cent) and forty-four females (30.6 per cent). This observation is borne out by previous studies. Musser and Herrmann in their study of forty-six cases of adherent pericarditis recorded that these occurred in males only.

A greater number of patients were in the later than in the earlier periods of life; sixty-eight (47.2 per cent) were in the sixth and seventh decades. One hundred eight patients (75 per cent) were between the ages of 30 and 70 years, the most productive period of life. The youngest patient was 2 years of age, had extensive parietal adhesions, and died of heart failure. The oldest patient was 85 years of age. The average age for all was 48.8 years.

Etiologic Conditions.—Definite etiologic diseases were determinable in seventy-three cases (50.7 per cent). Rheumatic fever occurred with greatest frequency; it was present in thirty-one cases (21.5 per cent). Rheumatic fever may have been an influence in other cases and not recognized, for previously identification of rheumatic fever rested chiefly on the presence of articular involvement, which is now known not to be a constant accompaniment.

Intrathoracic infection occurred next in frequency; twenty-five cases (17.4 per cent) were recorded.

Cardiac infarction occurred in nine cases (6.2 per cent). It is a condition that ordinarily is not accorded much consideration as a cause of adherent pericarditis. It is well known, of course, that cardiac infarction is frequently complicated by localized pericarditis overlying the region of myocardial destruction, a sterile inflammatory reaction. With healing of the infarct and recovery of the patient, the pericardial involvement resolves in the usual manner, with the result that a considerable portion of the pericardial sac becomes obliterated by fibrous adhesions.

Syphilis occurred as a possible etiologic disease in only four cases (2.8 per cent). In two of these cases, aortic aneurysm was present; in one, a dissecting aneurysm, with ultimate rupture into the pericardium, and in the other, a saccular aneurysm of the ascending portion. In both cases, the pericardial involvement could possibly have resulted from the

3. Musser, J. H., and Herrmann, G. R.: Chronic Pericarditis: The Clinical and Experimental Aspects, J. A. M. A. **87**:459 (Aug. 14) 1926.

mechanical effects of the aneurysms, whereas in the remaining two cases it is possible that some other infectious process may have been causal, although syphilis was the outstanding disease in the production of cardiovascular injury. The pericardial cavity was only partially obliterated in all of these cases.

Neoplastic invasion of the pericardium, with resulting pericardial reaction and partial obliteration of the sac, occurred in four cases (2.8 per cent). The invasion occurred through metastasis in two instances: in one case from a sarcoma of the stomach, and in the other, from a sarcoma of the left ovary. In two cases, the pericardium became involved by direct extension of a contiguous malignant tumor. A primary carcinoma of the left lung invaded the pericardium in one case, and an intrathoracic lesion of Hodgkin's disease in the other.

The intrathoracic infections comprised the following conditions: chronic obliterative pleuritis with involvement of the pericardium in fourteen cases (56 per cent), in two of which tuberculosis was present; chronic empyema with pleural and pericardial involvement in six cases (24 per cent); chronc mediastinitis in three cases (12 per cent); miliary tuberculosis with extensive invasion of the pericardium in one case (4 per cent), and purulent bronchitis with pulmonary abscesses in one case (4 per cent).

There were seventy-one cases (49.3 per cent) of adherent pericarditis in which definite evidence of etiologic diseases was not found. It seems probable that in numerous instances apparently trivial infections take place that result in acute fibrinous pericarditis; these conditions are not recognized at the time of their occurrence; they undergo spontaneous abatement, and ultimately result in partial or complete obliteration of the pericardial sac.

PATHOLOGIC DATA

The cases were divided into three groups according to the character of the pericardial involvement.

The pericardial sac was completely obliterated in fifty-three cases (36.8 per cent). In seventy-nine cases (54.9 per cent) the sac was partially obliterated, but in all of these instances to a considerable degree. The remaining twelve cases (8.3 per cent) were characterized by the presence of fairly extensive parietal adhesions to the surrounding structures.

Well marked calcification of portions of the pericardium occurred in fifteen cases (10.4 per cent). This phenomenon is probably the end-result of inflammatory disease. Case [4] stated that in such cases almost

4. Case, J. T.: Pericarditis Calculosa: Report of a New Case Discovered Roentgenologically, J. A. M. A. **80**:236 (Jan. 27) 1923.

without exception the visceral and parietal layers of the pericardium are united by a plastic process. In the present study, however, the pericardial sac was only partially obliterated in eight cases in which calcification was well marked, whereas the obliteration was complete in three. Calcification of the pericardium, evidenced in the life of the patient by means of roentgenography, has been reported by several authors, whose names will appear in the bibliography of a later article.

Weight of the Heart.—The weights in 107 cases (74.3 per cent) were available for study. Two cases were excluded from our computations, owing to inclusion of a greatly thickened pericardium in one case and inclusion of a metastatic growth in another. In table 1 are given the cardiac weights in the 105 remaining cases, grouped according to 100 Gm. spreads. In 87.7 per cent of the cases, the weights of the heart were in excess of normal. According to the studies of Smith,[5]

TABLE 1.—*Weight of the Heart in the One Hundred and Five Cases in Which It Was Known* *

Weight, Gm.	Cases	Percentage	
100–199	1	0.9	
200–299	12	11.5	
300–399	27	25.7	
400–499	21	20.0	
500–599	17	16.2	87.7 per cent
600–699	13	12.4	
700–799	6	5.8	
800–899	5	4.6	
900–999	3	2.9	

* Average cardiac weight, 478.1 Gm.

the average normal weight of the heart of the adult male is 294 Gm., whereas the average normal weight of the heart of the adult female is 250 Gm. The average weight of the heart in the group of cases under investigation was 478.1 Gm. The minimal weight of the heart was 135 Gm., whereas the maximal weight was 950 Gm.

If the cases are analyzed according to the three major pathologic groups, (1) complete obliteration of the pericardial sac, (2) partial obliteration of the pericardial sac and (3) parietal adhesions, very interesting differences in average cardiac weights appear (table 2).

These data in general are in agreement with those of Musser and Herrmann, who obtained average weights, in the three groups, of 536.6 Gm., 443 Gm. and 384 Gm. It must be remembered that the presence of cardiac hypertrophy in many of the cases was not solely the result of adherent pericarditis, for associated cardiac lesions existed that were also responsible for the increase in mass of muscle.

5. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, Am. Heart J. **4**:79 (Oct.) 1928.

Associated Cardiac Disease.—Associated disease of the heart occurred in seventy-seven cases (53.5 per cent). Lyter,[6] in a study of thirty cases of chronic pericardial adhesions, called attention to associated cardiac conditions.

The disease that occurred most frequently was coronary sclerosis; this was well marked in the thirty-one cases (21.5 per cent) recorded

TABLE 2.—*Weight of the Heart in All One Hundred and Five Cases in Which It Was Known, Classified on the Basis of Degree of Obliteration of Pericardial Sac*

	Complete Obliteration, 42 Cases		Partial Obliteration, 57 Cases		Parietal Adhesions, 6 Cases	
Weight, Gm.	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
100-199	..	....	1	1.8	..	....
200-299	6	14.3	4	7.0	2	33.3
300-399	11	26.2	13	22.8	3	50.0
400-499	8	19.0	11	19.3	1	16.7
500-599	6	14.3	12	21.0	..	....
600-699	7	16.7	6	10.5	..	....
700-799	1	2.4	5	8.8	..	....
800-899	2	4.7	3	5.3	..	....
900-999	1	2.4	2	3.5	..	....
Average weight	472.7 Gm.		506.5 Gm.		251.2 Gm.	

TABLE 3.—*Data Concerning Seventy-Seven Cases of Adherent Pericarditis in Which There Was Associated Cardiac Disease, Together with Sixty-Seven Cases in Which There Was Chronic Adherent Pericarditis Only*

Pathologic Diagnosis	Cases	Per Cent*	Average Age, Yr.	Average Cardiac Weight, Gm.†
Coronary sclerosis	31	21.5	61.3	542.8
Rheumatic heart disease (mitral stenosis)	25	17.4	37.0	478.1
Hypertensive heart disease	11	7.6	53.4	554.1
Rheumatic heart disease (aortic insufficiency)	6	4.2	27.6	891.0
Aortic syphilis	4	2.8	56.5	550.0
No associated cardiac disease	67	46.5	47.8	413.4

* The percentage is calculated on the basis of 144 (77 + 67). The total percentage of cases in which there was associated cardiac disease was 53.5.

† The average weight of the hearts in all cases in which there was associated cardiac disease, in which the weight of the hearts was known, was 536 Gm.

in table 3. The average degree of involvement was graded 3. Hypertension was present in eight of these thirty-one cases, healed cardiac infarction in five, recent cardiac infarction in four and the myofibrosis of gradual circulatory obliteration in four. This is not a complete record of all conditions associated with coronary sclerosis; for instance, some cases of rheumatic heart disease might be mentioned in this connection, but they are not, because the same cases are mentioned in the consideration of conditions associated with rheumatic heart disease.

6. Lyter, J. C.: Incidence, Associated Pathology and Clinical Diagnosis of Chronic Pericardial Adhesions, Am. J. M. Sc. **159**:891 (June) 1920.

The pericardium was completely obliterated in eleven of these thirty-one cases and partially obliterated in eighteen; parietal adhesions existed in two of them. The lowest cardiac weight was 230 Gm., and the greatest cardiac weight, 900 Gm. In order to determine the influence of hypertension on cardiac weight, the average weight of the hearts in the eight cases with hypertension was compared with the average weight of the hearts in the remaining twenty cases of coronary sclerosis. The average weight of the hearts in the cases with hypertension was 657.1 Gm.; in the cases without hypertension, 497.1 Gm. It must be recalled that the presence of adherent pericarditis materially influenced the cardiac weights in these groups. Also, Smith and Bartels[7] and others clearly showed that the heart that has survived infarction for a considerable period may increase its muscle mass. In the cases of healed and chronic infarction taken together, the average cardiac weight was 557.3 Gm., a figure greater than the average for the entire group of cases of coronary sclerosis. The age incidence of the cases of coronary sclerosis was of wide range; the youngest patient was 31 years of age, and the oldest, 85 years.

Rheumatic heart disease with mitral stenosis occurred next in order of frequency. The associated lesions in this group comprised one case each of the following: coronary sclerosis, graded 2; aortic insufficiency; aortic and tricuspid insufficiency, and aortic stenosis and hypertension. The pericardial sac was completely obliterated in nine cases and partially obliterated in fifteen cases; parietal adhesions were present in one case. The average cardiac weight was as it is given in table 3. The minimal cardiac weight was 280 Gm., and the maximal weight, 800 Gm. The youngest patient in this group was 10 years of age; the oldest, 73.

Hypertensive heart disease occurred in eleven cases (7.6 per cent). Complete obliteration of the pericardial sac was present in two cases, and in nine cases the obliteration was partial. The smallest heart weighed 300 Gm.; the largest, 930 Gm. The youngest patient was 22 years of age, and the oldest, 66.

Rheumatic heart disease with aortic insufficiency occurred in six cases (4.2 per cent). Five patients had associated mitral disease, although the aortic lesion dominated. In three cases there was complete obliteration, and in three, partial obliteration of the pericardial sac. The minimal cardiac weight was 832 Gm., and the maximal weight, 950 Gm. The weights of the hearts were greater in this group than in any other. The youngest patient was 6 years of age, and the oldest, 58.

7. Smith, H. L., and Bartels, E. C.: Coronary Thrombosis with Myocardial Infarction and Hypertrophy in Young Persons: A Report of Two Cases with Necropsy, J. A. M. A. **98**:1072 (March 26) 1932.

Aortic syphilis occurred in only four cases (2.8 per cent). These cases comprised one of aortitis with aortic insufficiency, one of dissecting aneurysm of the thoracic aorta with rupture into the pericardial cavity, one of aortitis and one of aortitis with aortic insufficiency and a saccular aneurysm of the ascending aorta. The pericardial sac was only partially obliterated in all cases. The lowest cardiac weight was 500 Gm., and the greatest, 600 Gm. The youngest patient was 38 years of age, and the oldest, 81.

Adherent pericarditis as the only cardiac disease occurred in sixty-seven cases (46.5 per cent). The pericardial cavity was completely obliterated in thirty cases (44.8 per cent). The obliteration was only partial in thirty-one cases (46.3 per cent), and parietal adhesions existed in six cases (8.9 per cent). The relationship of average cardiac

TABLE 4.—*Weight of the Heart in the Forty-Four Cases in Which It Was Known, of the Sixty-Seven Cases in Which Adherent Pericarditis Was the Only Cardiac Disease Present, Classified on the Basis of Degree of Obliteration of the Pericardial Sac*

	Complete Obliteration, 19 Cases		Partial Obliteration, 22 Cases		Parietal Adhesions, 3 Cases	
Weight, Gm.	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
100-199	..	....	1	4.5	..	....
200-299	3	15.8	3	13.7	2	66.7
300-399	8	42.2	7	31.8	1	33.3
400-499	3	15.8	6	27.3	..	....
500-599	3	15.8	2	9.1	..	....
600-699	1	5.2	1	4.5	..	....
700-799	..	....	2	9.1	..	....
800-899	1	5.2	..	....	..	....

weights in these major pathologic groups (based on degree of obliteration of pericardial sac) differs from that in the earlier portion of this paper, when the cases were analyzed regardless of associated cardiac disease. On recalling those figures (table 2), it is found that the greatest average cardiac weight occurred in the cases with partial obliteration of the pericardial sac (506.5 Gm.). In cases in which the sac was completely obliterated, the average weight of the hearts was less (472.7 Gm.), and in cases in which parietal adhesions existed, the smallest average cardiac weight was found (251.2 Gm.). However, when uncomplicated cases of adherent pericarditis are considered, cases in which other cardiac diseases capable of producing cardiac hypertrophy were not present, this relationship no longer obtains. There was practically no difference between the average weights of the hearts in cases in which the pericardial sac was partially obliterated, and in cases in which it was completely obliterated (table 4). In cases accompanied by parietal adhesions, however, the average weight of the hearts was lower. The latter group comprised only three cases, which permits a large ele-

ment of error, but the average weight is in general agreement with the larger series of cases. These figures indicate that the mechanical effect on cardiac hypertrophy of partial obliteration of the pericardial sac does not materially differ from that of complete obliteration. However, a considerable difference in effect is evident so far as parietal adhesions are concerned. It seems proper to conclude that complete and partial obliterations of the sac interfere with the action of the heart to a far greater degree than do parietal adhesions. The youngest patient of those with uncomplicated adherent pericarditis was 2 years of age, and the oldest, 73. The average age was 47.8 years, as has been seen in table 3. This closely approximates the average age of patients with associated cardiac disease, which was 47.1 years. In the cases in which adherent pericarditis was the only cardiac disease, and in which there was partial obliteration of the pericardial cavity, the fluid content was either increased in amount or altered in character in eighteen (22.7 per cent) of the cases in which the amount of fluid present was recorded. Clear fluid was found to be present in quantities varying from 40 to 1,000 cc. in six cases; pus was present in four cases, varying in amount from 5 to 300 cc., and the fluid was turbid or bloody in the remaining eight cases.

CLINICAL FEATURES

It is significant that in a group of 144 cases of adherent pericarditis in which necropsy revealed well marked involvement, only fifty-seven patients (39.5 per cent) presented complaints that made the heart the major issue in the clinical picture. This relatively small incidence is additional testimony to the fact that comparatively asymptomatic adherent pericarditis frequently exists, and is additional explanation of why many cases are overlooked in the course of the lives of the patients. Those patients who presented outstanding cardiac symptoms were to a large extent those who had associated cardiac disease. Of the fifty-seven patients, forty-seven (82.4 per cent) had associated cardiac disease, whereas only ten (17.6 per cent) had adherent pericarditis without any other pathologic condition of the heart. Only three cases of polyserositis were found in the entire group of fifty-seven. Among these cases in which cardiac symptoms and findings predominated, rheumatic heart disease with mitral stenosis occurred in nineteen cases. Other diseases in order of frequency were coronary sclerosis, sixteen cases; adherent pericarditis only, ten cases; rheumatic heart disease with aortic insufficiency, six cases; aortic syphilis, four cases, and hypertensive heart disease, two cases.

The eighty-seven cases in which adherent pericarditis was but an incidental, practically asymptomatic condition comprised a very miscellaneous group. Carcinoma was the outstanding disease in twenty-seven

of these cases (31 per cent); nephritis, in eight; sarcoma, in six; cholecystitis and septicemia, each in four; benign prostatic hypertrophy, pulmonary abscess, empyema and tuberculosis, each in three; tumor of the brain, adenomatous goiter with hyperthyroidism, ulcerative colitis, hepatic cirrhosis, chronic arthritis, ventral hernia and intestinal obstruction, each in two; perforated peptic ulcer, purpura hemorrhagica, calculi of the urinary bladder, psychosis, salpingitis, pernicious anemia, Hodgkin's disease, trifacial neuralgia, diabetes mellitus, bronchiectasis, cerebral hemorrhage and pneumonia, each in one.

There were no physical signs that occurred with sufficient uniformity to permit of their being considered characteristic of adherent pericarditis. Murmurs frequently occurred, but their time, quality, situation and transmission were not unusual, and they were largely present in cases with associated valvular disease. Pericardial friction rubs were audible in only eight cases.

Briefly reviewed, some of the signs that have been said to be characteristic of adherent pericarditis are as follows:

1. Kussmaul's [8] sign. The veins of the neck may fill during inspiration, accompanied by inspiratory diminution in the size of the pulse, and at times by absence of some beats during inspiration (pulsus paradoxus). This phenomenon is very occasionally observed.

2. Friedreich's [9] sign. By this is meant collapse of the veins of the neck, diastolic in time. This is not uncommon in heart failure resulting from various causes.

3. Broadbent's [10] sign. This consists in visible retraction of the back in the region of the eleventh and twelfth ribs, synchronous with cardiac systole. This sign, when present, is characteristic of parietal adhesions.

4. Cooper's [11] sign. This sign is elicited by determination of the length of time it is possible for the patient to hold the breath in inspiration, and, five minutes later, the same for holding the breath in expiration. Normal persons, it is said, can hold the breath in inspiration for from forty to seventy seconds, and in expiration for from twenty to twenty-five seconds. In case of heart disease, the values are said to be inspiration twenty-five seconds, and expiration fifteen seconds. In

8. Kussmaul, A.: Ueber schwielige Mediastino-Pericarditis und paradoxen Puls, Berl. klin. Wchnschr. **10**:433 (Sept. 15) 1873.

9. Friedreich, N.: Ueber den Venenpuls, Deutsches Arch. f. klin. Med. **1**:241 (Nov.) 1865.

10. Broadbent, W. H., and Broadbent, J. F. H.: Heart Disease, with Special Reference to Prognosis and Treatment, ed. 3, New York, William Wood & Company, 1900, p. 249.

11. Cooper, C. M.: The Respiratory Ratio: A Preliminary Note, J. A. M. A. **52**:1182 (April 10) 1909.

cases of mediastinal and pericardial adhesions, a paradoxical ratio is said to occur, namely, inspiration nine seconds, and expiration twenty-five seconds.

Roentgenography.—The heart was examined roentgenologically in fifty-four cases (37.5 per cent). Varying degrees of cardiac enlargement were found in thirty-four cases (62.9 per cent). There did not appear to be any characteristic contour; this, in part at least, was because the majority of patients subjected to this method of examination had associated cardiac disease, and the contour of the heart would naturally show the effect of the given lesion on the myocardium.

Electrocardiography.—When extensive fixation of the heart occurs, particularly by mediastinopericarditis and parietal adhesions, probably the most constant electrocardiographic feature is fixation of the electrical axis as shown by Dieuaide.[12]

TABLE 5.—*Electrocardiographic Findings in Forty-Nine Cases*

Findings	Adherent Pericarditis and Associated Cardiac Disease, Cases	Adherent Pericarditis Only, Cases
Auricular fibrillation	10	8
Auricular flutter	1	..
Extrasystolic arrhythmia	3	1
Complete heart block	1	..
Delayed auriculoventricular conduction	1	..
Incomplete bundle branch block	1	1
Significant T wave negativity	11	9
Change in contour and elevation of R-T segment	2	..

Electrocardiograms were obtained in forty-nine cases (34 per cent). Auricular fibrillation was the most frequent disorder of rhythm, occurring in eighteen cases (table 5). In three other cases in which electrocardiographic study was not made, auricular fibrillation was present, making its incidence in the entire group 14.5 per cent. This figure may be less than the actual incidence, for it is possible that arrhythmia may not have been mentioned in some of the earlier cases in which it occurred. It occurred in eight (80 per cent) of the cases in which adherent pericarditis only was present. The other findings are tabulated according to their occurrence. The incidence of significant T wave negativity in the cases of adherent pericarditis unassociated with other cardiac disease was high. In four of these cases there was T wave negativity in all leads.

The amplitude of the deflections in thirty-eight cases was carefully studied, and in general there was a lowering of amplitude of both the R and the T waves.[13] In all cases in which measurements were carried

12. Dieuaide, F. R.: The Electrocardiogram as an Aid in the Diagnosis of Adhesive Pericardial Mediastinitis, Arch. Int. Med. **35**:362 (March) 1925.

13. Normal amplitude of R wave = 10, 15 mm.; T wave = 3, 8 mm.

out, the greatest diminution ocurred in lead III. In cases in which obliteration of the pericardial cavity was partial, on the one hand, and cases in which it was complete, on the other, no appreciable differences in amplitude occurred. The average amplitude of the T waves was small in all leads. The figures were as follows: in lead I, 3.05 mm.; in lead II, 3.25 mm., and in lead III, 2.86 mm. The R waves were similarly relatively low: the average in lead I was 7.15 mm.; in lead II, 7.22 mm., and in lead III, 6.21 mm.

Mode of Death.—The heart was directly concerned with the death of the patient in fifty-seven cases (39.5 per cent). The predominant syndrome was that of congestive cardiac failure; it was recorded in thirty-nine cases (68.4 per cent). In twelve cases, death occurred very suddenly, and among these were nine cases of coronary disease.

TABLE 6.—*Comparison of Data in Cases in Which Death Was Caused by Heart Disease, with Those in Cases in Which It Was Caused by Other Conditions*

	Death from Cardiac Disease				Death from Other Causes			
Predominant Cardiac Condition, in Addition to Adherent Pericarditis	Cases	Per Cent	Average Cardiac Weight, Gm.	Average Age, Yr.	Cases	Per Cent	Average Cardiac Weight, Gm.	Average Age, Yr.
Rheumatic heart disease with mitral stenosis	19	76.0	489.6	31.6	6	24.0	435.0	53.5
Coronary sclerosis	16	51.6	719.9	57.0	15	48.4	451.7	66.0
Rheumatic heart disease with aortic insufficiency	6	100.0	891.0	27.6				
Aortic syphilis	4	100.0	550.0	56.5				
Hypertensive heart disease	2	18.1	700.0	56.5	9	81.9	535.8	52.7
No cardiac disease other than adherent pericarditis	10	14.9	619.0	43.7	57	85.1	367.9	48.6
Total and average	57	39.5	625.7	43.1	87	60.5	411.6	52.4

Detachment of mural thrombi resulting in fatal emboli occurred in four cases. Two patients died from subacute bacterial endocarditis (Streptococcus viridans).

Differences in data become evident when the essential findings in those cases in which patients died of heart disease are compared with those in cases in which the cause of death was unrelated to the heart (table 6).

The average weight of the heart among the patients who died of heart disease was 625.7 Gm., whereas in the group in which death was not related to heart disease, the cardiac weight was 411.6 Gm. The difference is 214.1 Gm. This appears to be important, and emphasizes the fact that the presence of a large heart is a significant prognostic sign. The average age of the patients who died from heart disease was 9.3 years less than that of the patients who died from other causes. The respective averages were 43.1 years as opposed to 52.4 years.

It is significant that 85.7 per cent of the patients with auricular fibrillation died of heart failure. Likewise, both the patients with

incomplete bundle branch block and those with complete heart block died as the result of heart failure.

Causes of death that were not concerned with the heart were as follows: Carcinoma, twenty-four cases; pneumonia, eight; nephritis, sarcoma, empyema and pulmonary embolism, six each; pyelonephritis and peritonitis, five each; septicemia, tumor of the brain, pulmonary abscess and ulcerative colitis, two each; perforated peptic ulcer, adenomatous goiter with hyperthyroidism, intestinal obstruction, psychosis, meningitis, cerebral hemorrhage, pyemia, purpura hemorrhagica, pernicious anemia, hepatic cirrhosis, diabetes mellitus and Hodgkin's disease, one each.

COMMENT

It becomes evident from this study that adherent pericarditis does not manifest its presence by a syndrome, nor by characteristic signs. The diagnosis of adherent pericarditis must be developed by composite analysis of symptoms and signs, each carefully considered and weighed in relation to the others.

Careful determination of etiologic factors demands considerable emphasis, and at times may be the only positive clue to identification of adherent pericarditis. The history of rheumatic fever should at once arouse suspicion, likewise the history of intrathoracic infection, healed cardiac infarction and intrathoracic cancer. The elicitation of symptoms indicative of previous pericarditis is, of course, almost positive evidence of partial obliteration of the pericardial cavity.

The presence of a large heart, in the absence of valvular lesions, of hypertension, of evidence of previous elevation of blood pressure, and of a clinical history that would indicate previous cardiac infarction, should at once suggest the possible existence of adherent pericarditis.

The presence of so-called classic signs of adherent pericarditis should receive full consideration, but their absence does not in any way justify failure to diagnose the disease. The presence of other cardiac disease does not minimize the probability of adherent pericarditis being present; in fact, it may frequently increase the probability of its existence. This is particularly true in rheumatic carditis. Only too often, identification of a cardiac lesion causes the examiner to believe that he has satisfactorily explained his patient's symptoms. This is detrimental to complete diagnosis, for it is almost the rule that cardiac lesions are multiple.

Fixation of the heart, as determined by physical examination and roentgenography, is important in identification of mediastinopericarditis and parietal adhesions. Unfortunately, so far as diagnosis is concerned, these cases are in the minority (8.3 per cent), and this sign fails completely in the majority of cases. The status is the same with regard to electrocardiography; fixation of the electrical axis is virtually confined

to the same group of cases. The presence of R and T waves of low amplitude in the electrocardiogram is suggestive of adherent pericarditis, but their occurrence in other diseases of the heart is well known and they cannot, therefore, be considered pathognomonic.

We wish particularly to stress the necessity for the development of a clinical sense of suspicion regarding the existence of adherent pericarditis in all cases of surmised or actual cardiac injury, and we are led to believe that adoption of such an attitude will distinctly decrease the large diagnostic error that prevails at the present time.

SUMMARY

One hundred and forty-four cases of adherent pericarditis in which the patients came to necropsy at the Mayo Clinic were studied with particular reference to clinical and pathologic correlation.

A marked predominance of the incidence in males occurred. Etiologic diseases occurred in the following order: (1) rheumatic fever, (2) intrathoracic infection, (3) cardiac infarction, (4) syphilis (certainly present, possibly etiologic) and (5) neoplastic invasion. The weights of the hearts were determined in 105 cases. The pericardium was partially calcified in fifteen cases (10.4 per cent).

Associated cardiac diseases occurred in seventy-seven cases (53.5 per cent). These in order of frequency were: (1) coronary sclerosis, (2) rheumatic heart disease with mitral stenosis, (3) hypertensive heart disease, (4) rheumatic heart disease with aortic insufficiency and (5) aortic syphilis.

The predominant clinical syndrome was referable to the heart in fifty-seven cases (39.5 per cent), and was in no manner related to the heart in eighty-seven cases (60.5 per cent). The latter comprised a miscellaneous group of diseases.

Death from heart disease occurred in 39.5 per cent of the cases, whereas the heart was not directly concerned with death in 60.5 per cent.

PERICARDITIS

II. CALCIFICATION OF PERICARDIUM

HARRY L. SMITH, M.D.
AND
FREDRICK A. WILLIUS, M.D.
ROCHESTER, MINN.

Calcification of the pericardium, also called "pericarditis calculosa," "concretio pericardii," "armored heart" and so forth, has been described by pathologists for many years. Scholz [1] mentioned that Morgagni published a report of a case of calcification of the myocardium in 1762, that Bordenave described a case in 1768, and that Simmons and Watson in 1783 published a report of a case, with an illustration. Schwartz,[2] in 1910, was probably the first to recognize this condition in the course of the life of the patient; he employed roentgenologic methods. Groedel [3] described a case in 1912 in which he made the diagnosis before death. A review of the literature by Case,[4] up to 1923, disclosed that in thirteen instances the condition had been recognized in the course of the life of the patient. Since Case's review, there have been reported in the literature twenty-one additional cases in which the diagnosis has been made in life,[5] a total of thirty-four cases so diagnosed.

From the Section on Cardiology, the Mayo Clinic.

1. Scholz, Thomas: Calcification of the Heart: Its Roentgenologic Demonstration. Review of Literature and Theories on Myocardial Calcification, Arch. Int. Med. **34**:32 (July) 1924. Radiographic Demonstrations of Calcification of the Myocardium During Life, J. Radiol. **5**:131 (April) 1924.

2. Schwartz, Gottwald: Wien. klin. Wchnschr. **23**:1823, 1910.

3. Groedel, F. M.: Erste Mitteilung über die Differenzierung einzelner Herzhöhlen im Röntgenbilde und den Nachweiss von Kalkschatten in der Herzsilhouette intra Vitan, Fortschr. a. d. Geb. d. Röntgenstrahlen **16**:337, 1911.

4. Case, J. T.: Pericarditis Calculosa. Report of New Case Discovered Roentgenologically, J. A. M. A. **80**:236 (Jan. 27) 1923.

5. Arnesen, J.: Case of Calcified Pericarditis (Panzerherz), Norsk mag. f. laegevidensk. **88**:688 (Aug.) 1927. Cutler, E. C., and Sosman, M. C.: Calcification in Heart and Pericardium, Am. J. Roentgenol. **12**:312 (Oct.) 1924. Desplats, R., and d'Hour, H.: Calcification du péricarde, J. de radiol. et d'électrol. **13**:45 (Jan.) 1929. Forman, F.: Case of Calcification of the Pericardium, J. M. A. South Africa **5**:271 (May 9) 1931. Guelke and Lommel: Herzbeutelresektion bei Concretio pericardii, Klin. Wchnschr. **4**:737 (April 16) 1925; abstr., J. A. M. A. **84**:1881 (June 13) 1925. Jones, H. W., and Roberts, R. E.: Calcification of the Pericardium, Brit. J. Radiol. **32**:167 (May) 1927. Läwen, A., and Matthes, M.:

and, as will be seen, we have one such case to add. Ninety-four cases of calcification of the pericardium in which necropsy was performed were reported in the literature, up to 1924.

The present study is drawn from the following material: fifteen cases in which the presence of calcification of the pericardium was proved at necropsy, and one case in which it was proved clinically. In addition, four cases are mentioned in which there was clinical evidence of calcification of the pericardium, but in which its presence was not proved. Among the fifteen subjects who came to necropsy, twelve were males and three, females. The youngest subject was 24 years of age, and the oldest, 84. The average age was 48.6 years.

PATHOLOGIC DATA

Chronic adherent pericarditis was present in all fifteen cases in which necropsy was performed. These were the only cases of calcification of the pericardium in 144 cases of chronic adherent pericarditis found in the course of 8,912 postmortem examinations. This is a somewhat higher incidence than that found by Wells;[6] he found four cases of calcification in 128 cases of adherent pericarditis, in 1,000 postmortem examinations. Chronic mitral endocarditis was present in four instances. Aortic and mitral endocarditis, aortic, mitral and tricuspid endocarditis,

---

Ein weiterer Fall von erfolgreich operierter Concretio pericardii, Deutsche med. Wchnschr. **54**:617 (April 13) 1928. LeGoff: Calcification du péricarde, Bull. et mém. Soc. de radiol. méd. de France **15**:329 (Dec.) 1927. Lenker, J. L.: Pericarditis calculosa, Pennsylvania M. J. **34**:89 (Nov.) 1930. Lossen, Heinz, and Kahl, Hermann: Ein Fall von Panzerherz, Zentralbl. f. Chir. **51**:2585 (Nov. 22) 1924. Pareja, J. M.: Algunas consideraciones clinicas con respecto a una observación de pericarditis callosa, Rev. méd. latino-am. **16**:519 (Jan.) 1931. Rainey, C. W.: Calcified Pericardium Occurring in a Patient with Peptic Ulcer, M. J. & Rec. **122**:212 (Aug. 19) 1925. Reed, C. O.: Calcification of the Pericardium, U. S. Vet. Bur. M. Bull. **4**:263 (March) 1928. Rusconi, M.: Un caso di pericarditis calculosa, Cuore e circolaz. **11**:485 (Dec.) 1927. Schlesinger, Hermann: Das Panzerherz, Med. Klin. **22**:11 (Jan. 2) 1926. Starck, Hugo: Zur Pathologie des Panzerherzens, ibid. **24**:1736 (Nov. 9) 1928. Stone, W. J.: Adherent Pericardium with Calcification, Am. Heart J. **1**:434 (April) 1926. Turner, H. H.: Calcification of the Pericardium. Report of Three New Cases with Review of the Literature, Internat. Clin. **4**:137 (Dec.) 1924. Vilvandre, G. E.: A Case of Calcification of the Pericardium, Lancet **1**:564 (March 15) 1930. Wells, H. G.: The Pathology of the Healed Fibrous Adhesions of the Pericardium, Am. J. M. Sc. **123**:241 (Feb.) 1902. Youmans, J. B.: Calcification of the Pericardium; a Clinical Problem; with Report of Two Additional Cases Diagnosed During Life, Ann. Clin. Med. **4**:1032 (June) 1926. Youmans, J. B., and Merrill, E. F.: Calcification of Pericardium: Report of Case Discovered Roentgenologically During Life, J. A. M. A. **82**:1833 (June 7) 1924.

6. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925.

syphilitic aortitis with aortic insufficiency, and coronary thrombosis with cardiac infarction occurred in one instance each.

The weight of the heart was recorded in twelve instances, and the average cardiac weight was 584 Gm. In two cases, the hearts were apparently of normal size. The pericardial sac was completely obliterated in eight instances and partially obliterated in seven.

Chronic pleuritis was present in four instances; hydrothorax in four; pulmonary infarction in two, and pyothorax in one. Evidence of tuberculosis was not present in a single case of the fifteen. In only four instances was there any significant pathologic change in the liver. In one of these, there was pigmentary cirrhosis of the liver; this was a case of hemochromatosis. In two cases there was "atrophic cirrhosis," and in one chronic passive congestion of the liver.

Fig. 1 (case 1 of the fifteen summarized).—Anterior aspect of the heart. The calcified pericardium is partially separated from the heart.

The degree of calcification varied from involvement of a few areas to involvement of the entire pericardium, with the exception of a small portion at the apex. This extreme condition was present in case 1 (figs. 1 and 2). In case 2, the pericardium was calcified moderately throughout, except at the apex. In case 3, the pericardium was calcified throughout, except a small area over the posterior surface of the right auricle. A brown, inspissated mass of old blood was partially calcified. Two mitral cusps contained rather marked deposits of calcium. In case 4, there were large, calcareous plaques over the right auricle and right ventricle. The aortic and mitral leaflets contained calcareous deposits. In case 5, there was a circumferential band of calcareous material in fibrous adhesions, just above the base of the heart. In case 6, there was extensive calcification posteriorly; one plaque measured 4 cm. in diameter. In case 7, there was an area of calcification on the posterior and

lateral surface of the left auricle; it measured 2 by 4 cm., and was 2 mm. thick. In case 8, there were calcified adhesions between the apex and the pericardial sac, and calcified areas on the anterior and posterior surfaces. In case 9, numerous calcified areas 1 by 3 cm. in diameter were found on the anterior surface of the ventricles. In case 10, fibrous adhesions with areas of calcification were present. In case 11, there

Fig. 2 (case 1 of the fifteen summarized).—Postmortem roentgenogram of the heart. Calcification is generally distributed.

were numerous areas of calcification in the pericardial adhesions and calcification in leaflets of the mitral valve; the chordae tendineae, also, were calcified. In case 12, adhesive pericarditis with areas of calcification was seen. In case 13, there were calcified areas in the superior and right aspects of the pericardium, one of which was 5 cm. in diameter and 5 mm. thick. In case 14, there was a calcified mass, 1 by 2 cm. in diameter, on the upper portion of the pericardium, reflected onto the

pulmonary artery. In case 15, there were several calcified areas on the right ventricle, each about 12 by 7 mm. in diameter.

There were several instances in which there was deposition of calcium in regions other than the pericardium: in three of these, marked deposits of calcium were found in the mitral valve; in one, in the aortic valve, and in one, in both the aortic and mitral valves. In one case, there were numerous gallstones, multiple calculi in the pancreatic ducts and multiple plaques in the diaphragm. Stones previously had been removed from the urinary bladder in one case. Marked coronary sclerosis occurred in two instances, and excessive aortic sclerosis once.

CLINICAL DATA

Roentgenograms of the thorax had been made in five of the cases in which necropsy was performed. In three of these instances, the heart was reported to be moderately enlarged, and in one, greatly enlarged; and in one the transverse diameter of the cardiac shadow was 18.5 cm. But in none of these fifteen cases was calcification of the pericardium recognized prior to necropsy.

In five of the fifteen cases, electrocardiographic studies were made. Auricular fibrillation was present in three cases, and significant changes in the T wave, in two. Ascites was present in four cases, in two of which it was present in marked degree, and in two, in moderate amount.

There were ten cases in which failure of the heart was the primary cause of death. The death of five patients was due to causes other than cardiac failure.

The diagnoses relative to the heart in eight cases were: chronic adhesive pericarditis, myocardial disease with cardiac failure, myocardial insufficiency, cardiac failure and syphilitic aortitis with aortic insufficiency, each in one case, and chronic rheumatic mitral endocarditis with mitral stenosis and insufficiency in three cases. The clinical diagnoses in the other seven cases were: bronze diabetes, carcinoma of the stomach, perforation of gastric ulcer, cirrhosis of the liver, carcinoma of the jejunum, perforation of the rectosigmoid and pyelonephritis.

In six of the fifteen cases there was a fairly definite history of rheumatic fever and in one case syphilitic infection was present.

As has been said (paragraph 2), there were four cases in which there was clinical evidence of calcification of the pericardium, but in which it was not proved. Evidence of calcification was found only incidentally. The patients had no symptoms that were referable to the heart. Two of them had chronic infectious arthritis; one, carcinoma of the colon, and one, chronic cholecystitis with stones. In one of the cases, roentgenologic examination revealed chronic bronchitis and fibrosis, and calcification of the margin of the pericardium; in one,

infiltration of the bases of both lungs and calcification of the left side of the pericardium; in one, a linear shadow of the left border of the heart, probably caused by calcification of the pericardium, and in one, bilateral tuberculosis with a small cavity and calcification of the left border of the pericardium.

In paragraph *2*, we stated that in one of our cases calcification of the pericardium was proved in life. This case will now be reported in detail.

REPORT OF CASE

A man, aged 45, came to the Mayo Clinic in August, 1929. He had nothing of medical significance to tell regarding his blood relatives. He had been married eighteen years, but his wife had not been pregnant. When he was 8 years of age, he had scarlet fever. In 1907, he was examined for postal service and was told that his heart was "not quite all right." He had influenza in 1918, underwent operation for hydrocele in 1921, and had influenza again in 1921. However, his general health was good until eight years before he came to the clinic; at that time, his ankles and legs began to swell. Soon after the onset of these symptoms, he noticed some dyspnea on climbing stairs and on severe exertion. These symptoms gradually increased in severity. In the few years before we saw him, he had an occasional pain in the lower left part of the thorax. He had experienced some palpitation. In the few months before his registration, he gained in weight. He had been able to continue his work in a bank.

Examination disclosed that the patient was well developed and well nourished. The blood pressure was 110 mm. of mercury systolic and 70 diastolic. The pulse rate was 100 beats each minute, and was totally irregular. The temperature was 98 F. Moderate dyspnea and considerable cyanosis were present. The veins in the neck were distended. Broadbent's sign was present. There was marked passive congestion at the bases of both lungs. Ascites was marked, and there was edema of the lower extremities. Cardiac dulness was slightly increased. Heart tones were distant, of poor quality and totally irregular.

Urinalysis gave essentially negative results. The concentration of hemoglobin and the number of erythrocytes were slightly less than normal. The Wassermann reaction of the blood was negative.

Roentgenologic examination (fig. *3 A*) gave evidence of old empyema of the lower right portion of the thorax, with rather marked retraction of the lower part of the right lung, with some pleuritic adhesions. The electrocardiogram disclosed that the cardiac rate was 74, and that auricular fibrillation was present. The Q-R-S complex was slurred in lead II and notched in lead III; there was evidence of slight right ventricular preponderance, and the T wave in derivation III was inverted. A diagnosis was made of chronic adhesive pericarditis, with congestive cardiac failure. The patient was placed in the hospital under a regimen for congestive cardiac failure, and abdominal paracentesis was done; 15,000 cc. of straw-colored fluid was removed. Ammonium nitrate and salyrgan, and digitalis, were administered to bring about diuresis, and the patient was dismissed from the hospital twenty-two days after his admission, greatly improved.

The second admission of the patient was in 1930, one year after the first. The findings were about the same as they were on his previous admission, except that congestive failure was more marked, and the heart was more greatly hypertrophied

(fig. 3 *B*). He was again placed in the hospital, on the same treatment as before. He underwent another abdominal paracentesis, and this time 11,000 cc. of straw-colored fluid was removed. He was dismissed thirteen days after admission, practically free from fluid, and his condition again was greatly improved.

The third admission was in 1931, one year after the second visit. In the interim, the patient had undergone abdominal paracentesis twice; 14,000 cc. of fluid was withdrawn one time, and 16,000 cc. another time. The patient's condition at this time was worse than it had been at any previous admission. The findings were essentially the same, but congestive failure was more marked, and roentgenologic examination of the thorax and especially of the heart (fig. 3 *C*) gave evidence of extensive calcification of the pericardium that had not been recognized on previous admissions. The patient was dismissed eleven days after admission, but with only moderate improvement.

Fig. 3 (case reported in detail).—*A*, roentgenogram taken in August, 1929; there is a small area of calcification along the left border of the pericardium; *B*, roentgenogram taken in August, 1930; the area of calcification is larger; *C*, roentgenogram taken in August, 1931; calcification is extensive.

COMMENT

Wells found the composition of calcified material to be nearly constant regardless of where the material is formed in the body. He found the composition to be 86 per cent calcium phosphate, 13 per cent calcium carbonate and 1 per cent magnesium phosphate. Barr [7] found deposits of calcium to be affected by a large number of factors, such as diminished blood supply, formation of necrotic tissue, degree of alkalinity of blood and tissues, the amounts of calcium and phosphates in the body, concentration of the blood, and presence and amount of vitamin C and of parathyroid hormone.

7. Barr, D. P.: Pathological Calcification, J. Missouri M. A. **27**:593 (Dec.) 1930.

Hewitt [8] has called our attention to the story of "Ethan Brand" by Nathaniel Hawthorne, which contains a vivid description of the death of the main character, who had a "heart of stone." The description is so vivid that one wonders if Hawthorne knew of a case. If not, it would be interesting to know the source of the tale. We feel that the story is so unique and so relevant that part of it is well worth quoting.

"With his long pole in his hand, he (Bartram) ascended to the top of the kiln. After a moment's pause, he called to his son.

"'Come up here, Joe!' he said.

"So little Joe ran up the hillock, and stood by his father's side. The marble was all burnt into perfect snow-white lime. But on its surface, in the midst of the circle, snow-white too, and thoroughly converted into lime, lay a human skeleton, in the attitude of a person who, after long toil, lies down to long repose. Within the ribs, strange to say—was the shape of a human heart.

"'Was the fellow's heart made of marble?' cried Bartram, in some perplexity at this phenomenon.

"'At any rate, it is burnt into what looks like special good lime; and, taking all the bones together, my kiln is half a bushel the richer for him.'

"So saying, the rude lime-burner lifted his pole, and, letting it fall upon the skeleton, the relics of Ethan Brand were crumbled into fragments."

SUMMARY AND CONCLUSIONS

Sixteen proved cases of calcification of the pericardium are considered; in fifteen of these cases, the diagnosis was established at necropsy, and in one case, in life. All of the sixteen patients had extensive chronic adhesive pericarditis. The diagnosis made in life was accomplished by roentgenologic examinations. Four other clinical cases are described, but the findings were not sufficiently striking for them to be classified as proved cases. The single etiologic factor that affected the largest number of patients was rheumatic infection. Tuberculosis was not present in any one of the proved cases; it was present in one of the four unproved cases. It would appear that calcification of the pericardium is a sequel of extensive chronic adhesive pericarditis and is an end-result of the same inflammatory process that produces chronic adhesive pericarditis. It is not a common condition, for it was found in only 15 of 144 cases of chronic adherent pericarditis found in the course of 8,912 postmortem examinations. Recognition of deposits of calcium in the pericardium by means of roentgen rays may be an aid in making the diagnosis of chronic adhesive pericarditis, which condition is extremely difficult to recognize.

8. Hewitt, R. M.: Nathaniel Hawthorne's Report of a Case of Pericarditis Calculosa, J. A. M. A. **98**:68 (Jan. 2) 1932.

PERICARDITIS

III. PERICARDITIS WITH EFFUSION

HARRY L. SMITH, M.D.
AND
FREDRICK A. WILLIUS, M.D.
ROCHESTER, MINN.

Under normal conditions, the pericardial sac contains a small amount of fluid, varying in quantity from 10 to 50 cc. The fluid is clear and light amber in color. In the presence of disease of the pericardium, or of congestive heart failure, the pericardial fluid may become altered in character and increased in amount. The alterations in the organism in cases of pericarditis with effusion are of one, or both, of two sorts: (1) a mechanical handicap is imposed on the heart by the presence of considerable fluid, and (2) if the effusion is the result of pericardial infection, there is sepsis or toxemia.

Pericardial effusion frequently is not recognized in life, and it has been stated that amounts of less than 150 cc. usually defy detection. This is, of course, not difficult to understand when one realizes the opportunity for concealment of fluid in the pericardial sac, if obstructing, adhesive processes are absent. The tendency for fluid to gravitate occurs here, as elsewhere, and therefore the fluid changes its position, depending on the patient's posture. Even moderate excess of fluid may be concealed when the patient is recumbent, because it gravitates to the posterior portion of the sac. When fluid is present in an amount completely to fill and distend the pericardium, its recognition is usually not difficult.

MATERIAL

Cases in which the amount of pericardial fluid was more than normal, or in which the fluid, irrespective of its amount, was altered in character, were selected for this study. There were 113 such cases, or 30 per cent of the cases of pericarditis in which necropsy was performed at the Mayo Clinic. The cases were grouped in the following manner: acute purulent pericarditis, seventy-seven cases (68.1 per cent of all cases of pericarditis with effusion); fibrinous pericarditis with effusion, thirty cases (26.5 per cent); tuberculous pericarditis, three cases (2.7 per cent), and noninflammatory effusion, three cases (2.7 per cent).

The predominance of the incidence in males was similar to that noted in the study of adherent pericarditis. Seventy-eight of the cases

From the Section on Cardiology, the Mayo Clinic.

occurred in males (69 per cent) and thirty-five in females (31 per cent). The patients represented practically all the decades of life. The youngest patient was aged only 8 months, whereas the oldest patient was aged 89 years. The average age was 43.5 years. The majority of the patients (72.5 per cent) were between the ages of 30 and 70 years.

ETIOLOGY

In considering the etiology of pericarditis with effusion, it is necessary to take up the cases in groups corresponding to the classifications given in the second paragraph preceding.

Acute Purulent Pericarditis.—Septic processes were the basis of purulent pericarditis in all of the seventy-seven cases. Intrathoracic infectious disease was apparently the primary condition in fifty-seven cases (74 per cent of the cases of acute purulent pericarditis), whereas sepsis elsewhere in the body occurred in twenty cases (26 per cent).

Thoracic empyema occurred with greatest frequency. It was present in twenty-eight cases, and was associated with bronchopneumonia in eleven cases and with lobar pneumonia in two. Bronchopneumonia without empyema occurred in ten cases, acute nontuberculous pleuritis in five, and multiple pulmonary abscesses and mediastinitis each in four cases. Other conditions which occurred less frequently were abscess of the liver with rupture into the pericardium in two cases, one of which was due to actinomycosis; pulmonary emboli with necrosis and infection in two cases; hepatic abscess with suppurative cholangeitis and thoracic extension, and carcinoma of the lung with abscess, in one case each. The remaining twenty cases resulted from remote sepsis, and included such diseases as gangrenous appendicitis with rupture, puerperal endometritis, scarlet fever, abscess of the brain and so forth.

Fibrinous Pericarditis with Effusion.—These thirty cases were characterized by the presence of nonpurulent fluid in excessive amounts, or by normal amounts of fluid of altered character. This group, to a large extent, represented cases of secondary nonpurulent pericarditis. Here, again, intrathoracic infectious disease predominated. It was present in twenty-one cases (70 per cent of the cases of fibrous pericarditis with effusion). Acute, nontuberculous pleuritis, which occurred in twelve cases, was the outstanding etiologic disease. Bronchopneumonia occurred in three cases and mediastinitis in two cases. Thoracic empyema occurred in three cases and was associated with bronchopneumonia and with lobar pneumonia in two of them. Aneurysmal erosion of the trachea, with inflammatory extension, was found in one case. Primary fibrinous pericarditis with effusion occurred in only nine cases (30 per cent).

Tuberculous Pericarditis with Effusion.—Only three cases of this condition were recorded. All were associated with tuberculosis of other portions of the body. A tuberculous abscess of the left suprarenal gland occurred in one case, pulmonary tuberculosis in one, and miliary tuberculosis in one.

Noninflammatory Effusion.—There were only three cases in this class. Two of the patients died of congestive heart failure; one had adherent pericarditis; the other, coronary disease. The third patient died as the result of pyelonephritis. The infrequent occurrence of this form of effusion may be explained, in part, by the effective modern treatment of edema by means of mercurial diuretics and ammonium nitrate. In the vast majority of instances, the retained fluid is readily excreted, and when death eventually occurs from heart failure, the serous cavities are relatively dry.

PATHOLOGIC DATA

Records of the weights of sixty of the hearts (53 per cent) of the entire series of 113 cases of pericarditis with effusion were suitable for pathologic study. In a number of cases such study could not be made: in some of these there were unusual cardiac weights, such as are met with in study of infants and small children, and in a few cases, the recorded weights included those of the entire pericardium.

Regardless of pathologic grouping, the weights of the hearts were as follows: between 100 and 199 Gm. in one case (1.7 per cent of sixty); 200 and 299 Gm. in eight cases (13.3 per cent); 300 and 399 Gm. in twenty-two cases (36.7 per cent); 400 and 499 Gm. in thirteen cases (21.7 per cent); 500 and 599 Gm. in eleven cases (18.3 per cent; 600 and 699 Gm. in four cases (6.6 per cent), and 700 and 799 Gm. in one case (1.7 per cent). The average cardiac weight was 426.8 Gm. In fifty-one cases (85 per cent of sixty) the cardiac weights were definitely in excess of normal, according to the standard of Smith.[1] He found that the average weight of normal hearts of adult males was 294 Gm., and that the average weight of normal hearts of adult females was 250 Gm. Cardiac weights in excess of 500 Gm. were found in sixteen cases. The heart of a small woman, 42 years of age, who had exophthalmic goiter weighed only 130 Gm. The greatest recorded weight was 750 Gm.: the patient was a man, 52 years of age, who had hypertension.

In analyzing the cases according to pathologic groups, certain differences in average cardiac weight appeared. The average weight of the

1. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, Am. Heart J. **4**:79 (Oct.) 1928.

hearts in the thirty-seven cases of purulent pericarditis in which the weights were known was 392.1 Gm. In this group, also, the majority of the cases (86.4 per cent) presented cardiac weights in excess of 300 Gm. The minimal cardiac weight was 130 Gm., whereas the maximal weight was 750 Gm. The weights of the hearts were between 100 and 199 Gm. in one case (2.7 per cent of thirty-seven); from 200 to 299 Gm. in five cases (13.5 per cent); from 300 to 399 Gm. in fifteen cases (40.5 per cent); from 400 to 499 Gm. in eleven cases (29.7 per cent); from 500 to 599 Gm. in three cases (8.2 per cent); between 600 and 699 Gm. in one case, and between 700 and 799 Gm. in one case (2.7 per cent respectively).

In nineteen cases of fibrinous pericarditis with effusion in which the cardiac weights were computed, the average weight was 454.4 Gm., 62.3 Gm. greater than in the cases of purulent pericarditis. In this group, again, the weight of most of the hearts (94.7 per cent) exceeded 300 Gm. The smallest recorded cardiac weight was 253 Gm., and the greatest, 650 Gm. In detail, the weights were from 200 to 299 Gm. in two cases (10.5 per cent of nineteen); from 300 to 399 Gm. in six cases (31.6 per cent); from 400 to 499 Gm. in two cases (10.5 per cent); from 500 to 599 Gm. in six cases (31.6 per cent), and from 600 to 699 Gm. in three cases (15.8 per cent).

The weight of the heart in the only case of tuberculous pericarditis in which it was recorded was 250 Gm. The heart was increased in weight in all the cases of noninflammatory effusion; the average weight was 466.6 Gm. The weights were 300, 525 and 575 Gm., respectively.

These analyses do not exclude primary cardiac disease, which when present contributes to cardiac hypertrophy. Further subdivisions are considered later in this study. Musser and Herrmann,[2] in their group of seventeen cases, comprising cases of acute and subacute serofibrinous or hemorrhagic pericarditis, found the average cardiac weight to be 363.2 Gm.

ASSOCIATED CARDIAC DISEASE

Other disease of the heart was associated with the pericarditis in only thirty-three cases (29.2 per cent of the 113 cases in the whole series). The incidence of associated disease was much smaller than that which was found in our study of adherent pericarditis.

In the present study of pericarditis with effusion, hypertensive heart disease occurred with greatest frequency among associated diseases; there were ten cases (8.8 per cent of the entire group of 113 cases). The average weight of the heart was 570.5 Gm.; the minimal weight was 415 Gm. and the maximal weight, 650 Gm. Purulent pericarditis

2. Musser, J. H., and Herrmann, G. R.: Chronic Pericarditis: The Clinical and Experimental Aspects, J. A. M. A. **87**:459 (Aug. 14) 1926.

and fibrinous pericarditis with effusion were of equal occurrence among these ten cases. The average age of the patients was 48 years. The youngest patient was 26 years of age, and the oldest, 59.

Rheumatic heart disease occurred next in frequency; eight cases were recorded (7.1 per cent of 113). The lesions, and their frequency, were as follows: mitral stenosis, three cases; aortic insufficiency, two cases; mitral stenosis and aortic insufficiency, one case; mitral stenosis and tricuspid insufficiency, one case. The average cardiac weight was 548.3 Gm. The smallest heart weighed 466 Gm.; the largest, 745 Gm. Purulent pericarditis occurred in six of these eight cases and fibrinous pericarditis with effusion in two cases. The average age of the patients was 41.5 years; the youngest patient was 10 years of age, and the oldest, 59.

Coronary sclerosis occurred in eight cases (7.1 per cent of 113). Acute cardiac infarction was noticed in three of these cases; in two cases, the infarction was the result of thrombosis, and in one, of embolism. Healed infarction was found in one case. Five cases presented evidence of previous or existent hypertension. The average cardiac weight was 538 Gm.; the minimal weight was 350 Gm., and the maximal weight, 750 Gm. The values in this group are undoubtedly increased by the influence of associated hypertension, although the degree of coronary sclerosis was so marked as to necessitate their inclusion in this classification. The pericarditis was of the purulent type in four cases, of the fibrinous type with effusion in two cases, and of the noninflammatory type with effusion, also in two cases. The average age of the patients was 58.6 years. The youngest patient was aged 48 years, and the oldest patient, 80 years.

Acute bacterial endocarditis occurred in five cases (4.4 per cent of 113). It was but an incident in septicemia in all of them. The average cardiac weight was 397.5 Gm.; the minimal weight was 325 Gm., and the maximal weight, 470 Gm. The pericarditis was of the purulent type in three cases, and of the fibrinous type, with effusion, in two cases. The average age was 49 years. The youngest patient was only 13 years of age, whereas the oldest was 67.

What was apparently an example of the heart in hyperthyrodism occurred in a man, 26 years of age, who had a hyperfunctioning adenomatous goiter. There was no evidence of preexistent hypertension, and the valves of the heart were normal. The heart weighed 525 Gm., and fibrinous pericarditis with effusion was present.

The remaining patient of the thirty-three who had cardiac disease associated with the pericarditis was a man, aged 62, who suffered from syphilitic aortitis, and who had a large saccular aneurysm of the innominate artery, with erosion and perforation of the trachea. The

pericarditis was of the fibrinous type with effusion. The weight of the heart was not recorded.

There were eighty cases (70.8 per cent of 113) of pericarditis unassociated with other cardiac disease. The average cardiac weight was 351 Gm., and was, as would be anticipated in this group, considerably less than that of any component of the group in which other cardiac disease was associated with pericarditis. Moreover, 351 Gm. is less than the average weight of the heart (537.8 Gm.) in all cases in which there was associated cardiac disease. In these eighty cases, the pericarditis was of the purulent type in fifty-nine, of the fibrinous type in seventeen, of the tuberculous type in three, and of the noninflammatory type in one. The average age of the patients was 52.2 years, three and a half years greater than that of patients who had cardiac disease associated with the pericarditis. The youngest patient was 8 months of age; the oldest, 85 years.

The weight of the hearts of twenty-six patients with purulent pericarditis was known. In one case (3.9 per cent of twenty-six) the cardiac weight was between 100 and 199 Gm.; in five cases (19.2 per cent), from 200 to 299 Gm.; in thirteen cases (50 per cent), from 300 to 399 Gm., and in seven cases (26.9 per cent), from 400 to 499 Gm.; the average weight was 348 Gm. Of eight cases of fibrinous pericarditis with effusion in which the cardiac weight was known, in one case (12.5 per cent of eight) the weight was between 200 and 299 Gm.; in four cases (50 per cent), from 300 to 399 Gm.; in two cases (25 per cent), from 400 to 499 Gm., and in one case (12.5 per cent), from 500 to 599 Gm.; the average weight was 379.7 Gm. In one case of tuberculous pericarditis, the cardiac weight was 250 Gm., and in one case of noninflammatory effusion, 300 Gm.

PERICARDIAL FLUID

Among the seventy-seven cases of purulent pericarditis in the series, the pericardial content was recorded in forty-one cases (53.2 per cent). The average content was 171.2 cc. The smallest amount was 10 cc., and the greatest, 750 cc. The amount of effusion present in the thirty cases of fibrinous pericarditis in the series was recorded in twenty-six cases (86.6 per cent). The average content was slightly greater than that in the cases with purulent pericarditis, 195.1 cc. The smallest amount of effusion was 25 cc.; the greatest, 500 cc. The pericardial content in the one case of tuberculous pericarditis in which it was determined was 1,500 cc. This quantity of fluid was aspirated a few days before death. The average pericardial content in the cases of noninflammatory effusion was 100 cc. The minimal quantity was 50 cc.; the maximal quantity, 150 cc.

ASSOCIATED PLEURAL FLUID

In eighty-three cases (73.5 per cent of 113) there was fluid in one or both pleural cavities. In the cases of purulent pericarditis, pleural fluid occurred in 81.8 per cent. The right pleural cavity contained fluid in twenty of these cases of purulent pericarditis; the left, in fourteen cases, and both pleural cavities, in twenty-nine cases. The average amount of fluid was 570.1 cc.; the smallest amount was 75 cc., and the greatest, 1,500 cc. Pleural fluid was present in 67 per cent of the cases of fibrinous pericarditis with effusion. The right pleural cavity contained fluid in eight of these cases; the left, in three, and fluid was present in both cavities in nine cases. The average content was 475 cc.; the smallest amount was 75 cc., and the greatest, 1,500 cc. Two patients with tuberculous pericarditis had pleural fluid. In both instances, the deposition was bilateral. The amount, in the one case in which it was recorded, was 150 cc. in each pleural cavity. In all cases of noninflammatory pericardial effusion there was hydrothorax. The distribution was unilateral in two cases and bilateral in one. The average content was 625 cc.; the minimal quantity was 100 cc., and the maximal, 1,200 cc.

CLINICAL FEATURES

Only fifteen patients (13.2 per cent of the entire 113 in the series) presented symptoms and signs predominantly of cardiac disease. Five cases in which pericarditis was of the purulent type included three cases of rheumatic heart disease, one case of coronary thrombosis and one case of coronary sclerosis. Among the patients with fibrinous pericarditis with effusion, associated cardiac disease was the dominant condition in seven. These comprised three with coronary sclerosis, two with rheumatic heart disease and two with hypertensive heart disease. In only one patient with tuberculous pericarditis were the cardiac features emphasized; there was an enormous effusion in this case. In two of the cases of noninflammatory effusion, the dominant clinical picture was that of congestive heart failure; one patient had adherent pericarditis, and the other, coronary sclerosis.

The cases represented a great variety of diseases. The predominant clinical observations in the seventy-seven cases of purulent pericarditis were as follows: carcinoma, in fourteen cases; hyperfunctioning adenomatous goiter and peptic ulcer, each in five cases; bronchopneumonia, benign prostatic hypertrophy, nephritis and exophthalmic goiter, each in four cases; abscess of the liver and rheumatic heart disease, each in three cases; lobar pneumonia, empyema, abscess of the lung, acute bacterial endocarditis, influenza, cholecystitis and appendicitis (ruptured), each in two cases, and trifacial neuralgia, Addison's disease, scarlet fever, puerperal endometritis, cicatricial stenosis of the common bile

duct, myelogenous leukemia, uterine fibromyoma, pyonephrosis, lacerated perineum, endothelioma of the dura, coronary thrombosis, coronary sclerosis, fracture of femur, pleuritis, miliary tuberculosis, hepatic cirrhosis and multiple abscesses of the brain, each in one case.

The predominant clinical observations in the thirty cases of fibrinous pericarditis with effusion were as follows: carcinoma and coronary sclerosis, each in three cases; rheumatic heart disease, malignant hypertension, acute bacterial endocarditis and nephritis, each in two cases, and abscess of the liver, hypertensive heart disease, peptic ulcer, diabetes mellitus, osteomyelitis of the femur, acute pleuritis, appendicitis (ruptured), hyperfunctioning adenomatous goiter, influenza, exophthalmic goiter, infectious arthritis, empyema, hernia, nephrolithiasis, syphilitic aortitis and bronchopneumonia, each in one case.

BLOOD PRESSURE

In considering the effect of pericardial effusion on blood pressure we included only those cases in which the pericardial content equalled or exceeded 150 cc. When the cases in which there were hypertension and aortic insufficiency had been excluded, twenty-three cases were available. The average readings of blood pressure were systolic, 121.8 mm.; diastolic, 70.2 mm., and pulse pressure, 51.6 mm. When the averages of blood pressure are considered according to pericardial content, a slight correlation is evident, although the number of cases is too small to permit definite conclusions to be drawn. In cases in which the pericardial content ranged from 150 to 199 cc., the average readings of blood pressure were systolic, 134.5 mm.; diastolic, 67.8 mm., and pulse pressure, 66.7 mm. In cases in which the pericardial fluid was present in amounts varying from 200 to 299 cc., the average values for blood pressure were: systolic, 124.5 mm.; diastolic, 78 mm., and pulse pressure, 46.5 mm. In cases in which the pericardial fluid was present in amounts of from 300 to 399 cc., the average readings were: systolic, 114 mm.; diastolic, 64.3 mm., and pulse pressure, 49.7 mm. In cases in which pericardial fluid was in the amount of from 600 to 650 cc., average readings were systolic, 110 mm.; diastolic, 71 mm., and pulse pressure, 39 mm. In cases in which pericardial fluid was present in amounts ranging from 700 to 750 cc., the average values were: systolic, 103.5 mm.; diastolic, 59 mm., and pulse pressure, 44.5 mm.

The average systolic pressure appears to drop in proportion to the amount of pericardial fluid present, and although the average pulse pressure tends to follow, the average diastolic values appear to fluctuate considerably.

SIGNS OF PERICARDIAL EFFUSION

Signs said to be characteristic of pericardial effusion are only infrequently encountered. As previously stated, it is impossible to deter-

mine the presence of less than 150 cc. of excess fluid. Probably the most reliable sign of effusion is the size and contour of the heart as determined by roentgenogram, particularly when considerable excess fluid has accumulated. It consists of bulging at the lower angles of the cardiac shadow, the region to which fluid gravitates, and as more fluid accumulates the grooves of the heart and great vessels become filled, giving a rounded shadow. The characteristic delineations of the normal heart are obliterated. This results in the so-called "water-bottle" shadow.

Pericardial rubs are frequently present in the early stages, but become obliterated when the pericardial surfaces become separated by the increasing quantity of fluid. Distant and muffled heart tones are suggestive of pericardial effusion, but their presence in greatly dilated hearts is well appreciated. Diminution or obliteration of the apex beat is suggestive of pericardial effusion.

Enlargement of the liver, with local tenderness, has been given as an early sign of pericardial effusion resulting from impingement on the orifices of the hepatic veins, which enter into the inferior vena cava. However, a tender, enlarged liver is the rule in congestive heart failure regardless of its type, and thus this sign becomes of minimal value so far as pericardial effusion is concerned.

Compression of the left lung (Ewart's[3] sign), occurring with extensive pericardial effusion, has been emphasized, and although important and worthy of consideration when present, occurs also with enormously enlarged hearts. Enormous effusions occasionally cause compression of the esophagus and trachea, producing dysphagia and respiratory obstruction.

Roentgenograms were obtained in thirty-four cases (30 per cent), and of these, nineteen gave evidence of varying degrees of cardiac enlargement. However, in only five cases was the shadow of the heart suggestive of effusion.

The electrocardiograms in twenty-four cases were available for study. Auricular fibrillation occurred in only four cases, in three of which there was associated cardiac disease. Auricular flutter occurred but once; there was associated cardiac disease in this case. Ten patients had significant T wave negativity, and eight of these had associated cardiac disease. Extrasystolic arrhythmia was present in five cases, in all of which there was associated cardiac disease.

---

3. Ewart, William: Practical Aids in the Diagnosis of Pericardial Effusion, in Connection with the Question as to Surgical Treatment, Brit. M. J. **1**:717 (March 21) 1896.

MODE OF DEATH

Death wholly as the result of cardiac disease was observed in only ten cases (8.8 per cent), of which two were cases of purulent pericarditis, six were cases of fibrinous pericarditis with effusion, and two were cases of noninflammatory effusion. Eighty-eight (77.9 per cent) of the patients died from sepsis. These cases comprised a miscellaneous group of conditions already discussed. Purulent pericarditis occurred in seventy-five cases and fibrinous pericarditis with effusion in thirteen cases. Death from other causes, such as hepatic cirrhosis, nephritis, pulmonary embolism, tuberculosis, and so forth, occurred in fifteen cases (13.3 per cent). In this group of fifteen were eleven cases of fibrinous pericarditis with effusion, three cases of tuberculous pericarditis and one case of noninflammatory effusion.

Summary of Causes of Death in the One Hundred and Thirteen Cases

Classification	Incidence of Given Causes of Death					
	Cardiac Disease		Sepsis		Other Causes	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Purulent pericarditis	2	2.6	75	97.4	0	0.0
Fibrinous pericarditis with effusion	6	20.0	13	43.3	11	36.7
Tuberculous pericarditis	0	0.0	0	0.0	3	100.0
Noninflammatory effusion	2	66.7	0	0.0	1	33.3

COMMENT AND SUMMARY

One hundred and thirteen cases of pericarditis with effusion in which necropsy was performed at the Mayo Clinic were studied with special reference to correlation of clinical and pathologic data. The cases were grouped according to the character of the effusion as follows: (1) acute purulent pericarditis, (2) fibrinous pericarditis with effusion, (3) tuberculous pericarditis and (4) noninflammatory effusion. A distinct predominance in males occurred. Infections were the etiologic factors in 111 cases (98.2 per cent). Intrathoracic infectious disease occurred with greatest frequency. Infectious processes elsewhere in the body occurred in thirty-one cases (27.4 per cent). Only two cases (1.8 per cent) were found in which infection was absent; both of these cases were examples of primary cardiac disease with congestive failure. From this study, therefore, it appears to be established that the presence of infectious intrathoracic disease offers a great chance of the pericardium being involved, and when infectious processes of the body as a whole are considered, the chance of pericarditis is still greater. Thus, the presence of infections should always focus attention on the pericardium, and the result may be that purulent pericarditis or fibrinous pericarditis with effusion will be recognized more commonly. It is also of interest

to observe the high incidence of pleural effusion occurring with these forms of pericarditis. Fluid was present in one or both pleural cavities in eighty-three cases (73.5 per cent). This observation may be applied as an accessory diagnostic sign that favors the probability of the presence of pericarditis.

The cardiac weights in the sixty cases in which these data were available are presented.

Associated disease of the heart occurred relatively infrequently in these cases of pericarditis with effusion. There were thirty-three cases (29.2 per cent) in which there was associated cardiac disease, which may be compared with 53.5 per cent of cases of adherent pericarditis [4] in which there was such associated disease.

The value of so-called characteristic signs of pericardial effusion is considerable and the presence of any such sign should be properly evaluated, but their absence does not justify failure of recognition of pericarditis with effusion. Complaints predominantly referable to the cardiovascular system occurred in only 13.2 per cent of the cases. The clinical syndrome in the majority of the cases was that of sepsis.

Death resulting directly and solely from heart disease occurred in only 8.8 per cent of the cases; from sepsis, in 77.9 per cent, and from other causes, in 13.3 per cent.

---

4. Smith, H. L., and Willius, F. A.: Pericarditis: I. Chronic Adherent Pericarditis, Arch. Int. Med., this issue, p. 171.

CHOLESTEROL OF THE BLOOD PLASMA IN HEPATIC AND BILIARY DISEASES

EMANUEL Z. EPSTEIN, M.D.
NEW YORK

As the liver is involved in a great many activities, it is not at all improbable that dissociated functional disturbances may arise when the organ is injured and that some functions are likely to suffer damage, whereas others remain intact or are only slightly affected. This may account for the invention of so many diverse liver function tests and the failure of any single one to satisfy the need for a uniformly accurate method of determining the functional capacity of the diseased liver. The studies have been directed toward the variations in the normal excretory and metabolic processes with which the liver is concerned. In addition, attempts have been made to evaluate the condition of the organ by increasing the burdens in tolerance tests with sugars, fats and proteins, as well as injection of pigments, exogenous substances such as dyes, cinchophen, etc. A discussion of the value of all these functional probes would be too involved. Summaries and reviews on the subject have been given by Rich,[1] Greene, Snell and Walters,[2] Schöndube,[3] Schrumpf,[4] and others, without uniformity in the conclusions. Recently several aspects of the problem have been reported. Shay, Schloss and Rodis [5] revived the Bauer galactose tolerance test as a means of early differentiation of the group of toxic or infectious jaundice. Lichtman and Sobotka [6] evolved a new method of determining tyrosine in the urine by means of the enzyme tyrosinase. Lichtman [7] utilized the ability

From the Medical Division (Dr. George Baehr) and the Laboratories of Mount Sinai Hospital.

1. Rich, A. R.: Bull. Johns Hopkins Hosp. **47**:338, 1930.

2. Greene, C. H.; Snell, A. M., and Walters, Waltman: Diseases of the Liver: I. A Survey of Tests for Hepatic Function, Arch. Int. Med. **36**:248 (Aug.) 1925.

3. Schöndube, W.: Deutsche med. Wchnschr. **56**:878 (May 23); 922 (May 30); 965 (June 6) 1930.

4. Schrumpf, A.: Ztschr. f. klin. Med. **116**:449, 1931.

5. Shay, H.; Schloss, E. M., and Rodis, I.: II. The Galactose Tolerance Test in the Differential Diagnosis of Jaundice, Arch. Int. Med. **47**:650 (April) 1931.

6. Lichtman, S. S., and Sobotka, H.: J. Biol. Chem. **85**:261, 1929.

7. Lichtman, S. S.: Cinchophen Oxidation Test of Function of Hepatic Cells, Arch. Int. Med. **48**:98 (July) 1931.

of the liver to oxidize cinchophen, previously ingested, as an index of hepatic function. Bernheim [8] employed the intravenous injection of distilled water and the subsequent icterus index values as a liver function test. In 1927, von Bergmann [9] introduced the bilirubin tolerance test, injecting the pigment into the blood stream and studying the rate of elimination by the liver as an index of hepatic function. Eilbott,[10] his pupil, amplified the work, and recently Harrop and Barron [11] reported its utilization as a test for liver insufficiency.

In recent years, considerable attention has been focused on the rôle of the liver in the cholesterol metabolism. According to the most recent reviews by workers on the subject—Hueck,[12] Thannhauser,[13] Gardner and Gainsborough,[14] Schönheimer,[15] Bürger,[16] etc.—the values of the cholesterol in the blood plasma of human beings represent the resultant of many factors. It is agreed that the greatest source of the cholesterol in the body is exogenous, and that this alimentary absorption depends on the amount of cholesterol in the ingested food and the presence of fatty acids, bile and pancreatic juices in the intestines. There are, however, several endogenous sources which include the destruction of erythrocytes and other body cells, the now accepted synthesis of cholesterol by the organism, and its mobilization from the fat tissue stores and the reticulo-endothelial cells. According to Thannhauser, the liver is the main excretory organ of cholesterol and regulates the relative content of the blood in cholesterol and cholesterol ester (the compound of one molecule of cholesterol with one molecule of a fatty acid). One hundred cubic centimeters of normal human plasma contains from 150 to 200 mg. of total cholesterol, of which from 50 to 70 per cent is in the form of cholesterol ester.

As early as 1862, Austin Flint, Jr.,[17] described a new excretory function of the liver which consisted of the removal of cholesterol from the blood, and believed that hypercholesteremia depended on pathologic changes in the liver. He also observed hypercholesteremia with obstructive lesions in the biliary tract, a fact noted in more recent years by

8. Bernheim, A. R.: Proc. Soc. Exper. Biol. & Med. **25**:675, 1928.
9. von Bergmann, G.: Klin. Wchnschr. **6**:776, 1927.
10. Eilbott, W.: Ztschr. f. klin. Med. **106**:529, 1927.
11. Harrop, G. A., Jr., and Barron, E. S. G.: J. Clin. Investigation **9**:577, 1931.
12. Hueck, W.: Zentralbl. f. Path. u. path. Anat. **36**:211, 1925.
13. Thannhauser, S. J.: Lehrbuch des Stoffwechsels und der Stoffwechselkrankheiten, Munich, J. F. Bergmann, 1929.
14. Gardner, J. A., and Gainsborough, H.: Quart. J. Med. **23**:465, 1930.
15. Schönheimer, R.: Ztschr. f. physiol. Chem. **185**:119, 1929. Schönheimer, R.; von Behring, H.; Hummel, R., and Schindel, L.: ibid. **192**:73, 1930.
16. Bürger, M.: Ergeb. d. inn. Med. u. Kinderh. **34**:583, 1928.
17. Flint, A., Jr.: Am. J. M. Sc. **44**:305, 1862.

Chauffard, Laroche and Grigaut,[18] Beumer and Bürger,[19] Feigl,[20] Bang,[21] Stepp,[22] Rothschild and Felsen,[23] Chauffard,[24] and others. Feigl, using the Bloor method, reported cholesterol values as high as 1,100 mg. in 100 cc. of blood plasma. Rothschild and Felsen and Stepp noted a direct relationship between the degree of jaundice and cholesteremia in pure, uncomplicated cases of obstructive jaundice. Exceptions to this were noted by Stepp, when factors of cachexia and poor fat resorption supervened over a longer time, and by Rothschild and Felsen, when high temperatures and infection occurred. Furthermore, the latter investigators made an important observation, that in other conditions associated with jaundice-cirrhosis of the liver, acute yellow atrophy, pernicious vomiting of pregnancy—the cholesteremia bore no relation to the intensity of the jaundice. This differentiation, later confirmed by many others, has served an important clinical purpose.

Although Feigl [25] reported low cholesterol ester values in a study of the blood lipoids in acute yellow atrophy, he did not attach any special significance to the observations. Thannhauser and Schaber,[26] later, showed that in cases of damage of the liver the values for cholesterol ester were below those of the free cholesterol, and in the more severe cases (acute yellow atrophy) the esters were much depressed or absent. To this drop in cholesterol esters they attached the name "Estersturz," and attributed the phenomenon to a disturbance in the liver of the synthesis of cholesterol ester from fatty acids and free cholesterol and of the hydrolysis of cholesterol esters into free cholesterol and fatty acids. They consider this reversible reaction dependent on the enzymes of the liver cells, which are disturbed in diffuse parenchymatous lesions. This "Estersturz" was interpreted as indicating liver damage. In disagreement with these authors, Bürger and Habs,[27] Stern and Suchantke,[28] and Gardner and Gainsborough [14] did not accept this hypothesis, and considered the drop in ester values to be dependent on the failure of fat

18. Chauffard, A.; Laroche, G., and Grigaut, A.: Compt. rend. Soc. de biol. **73**:23, 1912.

19. Beumer, H., and Bürger, M.: Ztschr. f. exper. Path. u. Therap. **13**:343, 1913.

20. Feigl, J.: Biochem. Ztschr. **90**:1, 1918.

21. Bang, I.: Biochem. Ztschr. **91**:122, 1918.

22. Stepp, W.: Beitr. z. path. Anat. **69**:233, 1921.

23. Rothschild, M. A., and Felsen, J.: The Cholesterol Content of the Blood in Various Hepatic Conditions, Arch. Int. Med. **24**:520 (Nov.) 1919.

24. Chauffard, A.: La lithiase biliare, ed. 2, Paris, Masson et Cie, 1922.

25. Feigl, J.: Biochem. Ztschr. **86**:1, 1918.

26. Thannhauser, S. J., and Schaber, H.: Klin. Wchnschr. **5**:252, 1926.

27. Bürger, M., and Habs, H.: Klin. Wchnschr. **6**:2221, 1927.

28. Stern, R., and Suchantke, G.: Arch. f. exper. Path. u. Pharmakol. **115**:221, 1926.

resorption. They maintained that the absence of fat resorption from the intestines obliges the body to deesterize the combined cholesterol in the plasma in order to be able to utilize the fatty acid.

Adler and Lemmel,[29] in a very extensive study of the blood cholesterol in various hepatic and biliary conditions, agreed with Thannhauser and Schaber that the functions of the liver are intimately related to the regulation of: the ratio of total to ester cholesterol in the blood, fat mobilization and movement, excretion and synthesis of cholesterol. Through simultaneous investigations of other liver functions, they have concluded that the disturbed cholesterol picture parallels most disturbances in other functions of the liver and reflects parenchymatous liver disease.

I [30] found the cholesterol ester values in the blood plasma to be greatly diminished, and even nil, in cases of severe liver disease, and observed them return to normal with improvement in the clinical picture. In these cases, bile and urobilin were present in the stools, even when the ester values were very low, so that the theory of disturbed fat and cholesterol resorption as an explanation cannot entirely account for the phenomenon in cases of primary liver diseases. My observations support the theory of Thannhauser that the "Estersturz" is the result of diffuse damage to the liver. For the past two years, I have also been interested in the blood cholesterol in cases of jaundice of various causes, making repeated observations throughout the entire clinical course from the time of admission to the hospital until the termination of the condition. It was hoped that a complete picture might provide a rational understanding of the value of the blood cholesterol partition in the various types of jaundice, and might also explain possible discrepancies.

Determinations of the total, free and ester cholesterol content of the blood were carried out on 1 cc. of blood plasma taken from the patients in the morning before breakfast. Specimens obtained during fasting were utilized because of the work of Gardner,[31] who showed that changes in the cholesterol content of the plasma, as well as in the relation of ester to total cholesterol, occurred during the digestive process. Gardner could not explain these changes on an influx of the cholesterol absorbed from the alimentary canal, but considered them as evidence of an active endogenous metabolism during digestion, in which cholesterol takes some part. I have employed the method of Bloor and Knudson [32] for my determinations. The work was carried out under

29. Adler, A., and Lemmel, H.: Deutsches Arch. f. klin. Med. **158**:173, 1928.

30. Epstein, E. Z.: The Cholesterol Partition of the Blood Plasma in Parenchymatous Diseases of the Liver, Arch. Int. Med. **47**:82 (Jan.) 1931.

31. Gardner, J. A., and Gainsborough, H.: Biochem. J. **22**:1048, 1928.

32. Bloor, W. R.: J. Biol. Chem. **24**:227, 1916. Bloor, W. R., and Knudson, A.: ibid. **27**:107, 1916.

the constant supervision and with the invaluable aid and suggestions of Dr. George Baehr of the Medical Division and of Dr. Harry Sobotka of the Chemical Laboratory.

OBSTRUCTIVE JAUNDICE

Table 1 summarizes the findings in the blood, urine and feces, as well as the operative and necropsy reports in forty-three cases of obstruction to the common bile duct by neoplasms, stones, strictures, carcinomatous glands, etc. In the great majority of instances a pronounced hypercholesteremia was found, which roughly paralleled the amount of blood pigment and the degree of occlusion of the common bile duct. The degree of increase in blood cholesterol varied. The maximum concentration was more than 900 mg. per hundred cubic centimeters.

The hypercholesteremia accompanying obstructive jaundice is explained by the work of Eppinger,[33] and Barron and Bumstead,[34] who showed that with impediments to the proper outflow of bile, the bile canaliculi become distended, tortuous and frequently ruptured as a result of the back pressure of the biliary stasis. This results in the outpouring of the bile into the pericapillary lymph spaces and blood stream. Rich, in his exhaustive review,[1] called this the regurgitative type of jaundice. Not only the biliary pigments and acids but concomitantly the cholesterol of the bile are thrown back into the circulation. With the removal of the obstruction, the hypercholesteremia and hyperbilirubinemia lessen and disappear, although the former may persist for a considerable time after the jaundice has cleared up.

This regurgitative hypercholesteremia, which occurred in the majority of cases, was only slight or even lacking in eight instances, although a considerable hyperbilirubinemia was present. The failure of the cholesterol level to parallel the degree of jaundice in all instances was thought to be due to infection, superimposed on the obstruction, cachexia, cholemia and damage to the liver incident to long continued biliary stasis. However, cases 1, 5, 16, 22, 27 and 34 illustrate that hypercholesteremia may occur in spite of cachexia, cholemia, infection and long-standing biliary stasis.

One observes from table 1 that in about half of the cases of obstructive jaundice the ester values rose in proportion to the increase in total cholesterol. In other instances there was an absolute but not a proportionate increase of ester. And in cases 5, 6, 7, 13, 16, 21, 39 and 40, the cholesterol ester was lowered, in spite of the pronounced

33. Eppinger, H.: Beitr. z. path. Anat. u. z. allg. Path. **31**:230, 1902.

34. Barron, E. S. G., and Bumstead, J. H.: J. Exper. Med. **47**:999, 1928.

TABLE 1.—*Obstructive Jaundice*

Case	Age	Sex	Duration Jaundice Before Admission	Date	Urine		Stool		Blood			Cholesterol, Mg. per 100 Cc.				Observations
					Bile	Urobilin	Bile	Urobilin	Icterus Index	Van den Bergh Direct	Van den Bergh Indirect	Total	Ester	Free	Ester, per Cent	
1	60	F	6 wks.	2/21	+	0	0	0	125	Pr. +	1:15,000	520	175	345	34	Carcinoma of head of pancreas; cachexia
2	52	F	8 wks.	2/21	+++	Ft. tr.	0	+	...	Pr. +	1:14,000	312	70	242	22	Carcinoma of head of pancreas
3	36	F	1 day	7/22	+	..	++	Trace	...	Del. +	1:65,000	365	219	146	60	Operation: stones in common bile and hepatic ducts
4	32	F	1 mo.	3/26	+	Trace	0	0	100	Pr. +	1:23,000	224	106	118	47	Operation: carcinoma of head of pancreas; cholemia; death 4 days postoperatively
5	70	M	4 mos.	6/24	+++	+	0	+	200	Pr. +	1:7,000	750	50	700	7	Carcinoma of head of pancreas; painless jaundice; enlarged, irregular liver; cachexia
6	32	M	5 wks.	7/21	+	++	0	0	...	Pr. +	1:30,000	800	90	710	11	Autopsy: adenocarcinoma of rectum; infiltration and occlusion of common bile duct by surrounding metastatic hilus nodes
				7/28	+	..	0	0	...	.....	.....	680	92	588	14	
				8/ 5	+++	0	+	..	...	.....	.....	520	72	448	14	
				8/14	+++	0	0	..	150	.....	.....	586	36	550	6	
7	52	M	9 mos.	9/ 3	++	+	0	Ft. tr.	85	Pr. +	1:13,000	536	62	474	11	Autopsy: carcinoma of head of pancreas with stenosis of papilla of Vater
8	40	F	4 wks.	11/ 5	++	+	0	0	...	Pr. +	1:15,000	470	268	202	57	Operation: carcinoma of head of pancreas with metastases to liver
9	62	F	3 days	11/11	+	..	..	Trace	...	Del. +	1:20,000	586	346	240	59	Operation: very large stone obstructing common bile duct
10	55	M	7 wks.	11/17	++	0	0	0	180	Pr. +	1:7,000	340	85	255	25	Carcinoma of head of pancreas with liver metastases and common bile duct obstruction
11	60	M	1 wk.	11/10	+++	+	..	..	...	Pr. +	1:50,000	536	288	248	54	Operation: stone obstructing common bile duct
12	38	M	2 mos. remittent	12/16	+	+	+	+	55	Pr. +	1:25,000	416	190	226	46	
				12/26	+++	+	..	Trace	65	Pr. +	1:25,000	750	470	280	63	
				1/ 3	Trace	+	..	+	40	.....	.....	830	360	470	43	
				1/ 8	0	0	..	0	30	Del. +	1:300,000	625	375	250	60	
				1/16	0	0	..	..	16	.....	.....	288	225	63	78	
				2/ 3	..	..	..	..	17	.....	.....	280	150	130	53	
				2/ 9	++	+	..	..	30	.....	.....	695	375	320	54	
				2/28	+	++	..	+	75	Pr. +	1:25,000	750	375	375	50	Operation: obstruction of common bile duct; carcinoma of papilla of Vater; metastases to liver

13	53	M	1 mo.	1/ 9 1/13	+++ ++++	Trace 0	.. ..	Trace Ft. tr.	140 175	Pr. + Pr. +	1:8,000 1:8,000	272 310	32 Trace	240 ±310	12	Autopsy: carcinoma of gallbladder; metastases to lymph nodes at porta hepatis with infiltration of wall of common bile duct and subsequent stenosis; subacute purulent cholangeitis with multiple liver abscesses
14	69	M	10 wks.	1/20	++	++	..	..	45	Pr. +	1:40,000	312	208	104	66	Operation: stone removed from common bile duct
				2/ 5	+++	+++	..	..	100	Pr. +	1:15,000	214	80	134	37	Cholemia
15	48	F	6 wks.	2/ 5	+	++	..	..	40	.....	.....	535	415	120	77	Carcinoma of rectum (postoperative); metastases to porta hepatis
16	64	F	.....	4/30	0	++++	..	++	...	Pr. +	1:50,000	480	40	440	8	Operation: large common bile duct stone
				5/10	0	++++	..	..	45	Pr. +	1:50,000	420	52	368	12	Autopsy: purulent cholangeitis and cholangeitic hepatitis; parenchymatous degeneration of liver
				5/16	..	+	..	..	36	.....	.....	416	Trace	±416		
17	66	F	2 wks.	5/20	++	0	..	0	150	Pr. +	1:14,000	750	234	516	31	Operation: carcinoma of papilla of Vater
				5/26	+++	0	..	Very ft. tr.	...	.....	.....	600	214	386	35	
				6/ 4	..	..	..	..	...	.....	.....	226	30	196	13	Tube in common bile duct with drainage for 12 days
18	70	F	1 wk.	12/11	++++	+++	0	0	65	Pr. +	1:17,000	312	108	204	34	Abdominal malignancy; metastases to hilus lymph nodes
				12/19	+	+	..	+	50	Pr. +	1:22,000	312	190	122	60	
19	58	M	.....	12/ 9	+++	++	Trace	+	50	Pr. +	1:35,000	330	...	...	..	Autopsy: common bile duct stone occluding papilla of Vater; obstructive biliary cirrhosis; septic course
				12/26	+	++	..	..	40	Pr. +	1:62,000	290	104	186	36	
				1/ 9	..	..	..	..	...	.....	.....	156	80	76	51	
				1/16	..	..	..	..	105	Pr. +	1:30,000	130	90	40	69	
20	52	F	5 wks.	2/13	++++	+	+	+	160	Pr. +	1:30,000	394	208	186	53	Operation: numerous stones in common bile duct
21	44	F	2 days	4/30	+	0	0	0	60	Pr. +	1:50,000	250	25	225	10	Operation: stone in common bile duct; drainage of common bile duct
				5/26	..	..	..	..	50	.....	.....	245	82	163	33	
				6/ 6	..	..	..	+	...	.....	.....	170	45	125	26	
22	70	M	6 mos.	4/14	+	+	..	..	150	Pr. +	1:30,000	445	75	370	17	Carcinoma of head of pancreas; painless jaundice, weakness, loss of weight; liver large, irregular and nodular; distended gallbladder; cachexia
				4/24	++	..	..	..	125	.....	.....	255	150	105	59	
23	56	M	3 mos.	4/ 8	+++	Ft. tr.	..	..	120	Pr. +	1:17,000	935	625	310	67	Carcinoma of stomach (postoperative); metastases to liver; obstructive jaundice due to metastatic nodes
24	60	M	3 wks.	7/ 1	++	0	..	+	50	Pr. +	1:30,000	220	80	140	36	Operation: large stone in common bile duct
				8/ 4	..	..	..	..	...	Pr. +	1:30,000	268	136	132	50	

TABLE 1.—*Obstructive Jaundice—Continued*

Case	Age	Sex	Duration Jaundice Before Admission	Date	Urine		Stool		Blood			Cholesterol, Mg. per 100 Cc.				Observations
					Bile	Urobilin	Bile	Urobilin	Icterus Index	Van den Bergh Direct	Van den Bergh Indirect	Total	Ester	Free	Ester, per Cent	
25	60	M	2 wks.	4/14	++++	0	..	0	...	.....	.....	625	415	210	66	Autopsy: carcinoma of gallbladder and cystic duct with extension into duodenum and common bile duct with subsequent stenosis of latter
26	43	M	2 wks.	4/ 2	+	0	..	Very ft. tr.	42	Pr. +	1:50,000	375	90	285	24	Operation: carcinoma of head of pancreas
27	55	M	3 wks.	2/27	+++	+++	..	+	110	Pr. +	1:16,000	680	468	212	66	Autopsy: complete occlusion of papilla of Vater by calculus; purulent cholangeitis; severe hepatitis
				3/ 2	..	..	..	..	60	.....	.....	935	625	310	67	
				3/11	+++	++	..	+	48	Del. +	1:100,000	625	375	250	60	
				3/24	++	++	..	..	70	Pr. +	1:14,000	658	428	230	66	
28	41	F	10 days	4/10	+++	Trace	..	..	75	.....	.....	575	235	340	40	Operation: three large stones completely occluding common bile duct
				4/21	+	Trace	..	..	45	Del. +	1:50,000	625	470	155	75	
29	43	M	3 wks.	1/29	+	0	+	++	35	Del. +	1:90,000	355	150	205	42	Operation: carcinoma of gallbladder; metastases to lymph nodes in omentum and porta hepatis
				2/ 5	Ft. tr.	+++	..	..	25	.....	.....	536	288	248	54	
				3/ 6	..	..	..	..	...	Neg.	1:100,000	340	270	70	79	
30	50	M	10 wks.	1/20	+	+	..	..	45	Pr. +	1:40,000	312	208	104	66	Operation: large common bile duct stone
				2/ 5	+++	+++	..	..	100	Pr. +	1:15,000	214	80	134	37	Cholemia
31	73	F	6 wks.	5/ 4	Ft. tr.	Ft. tr.	..	+	25	Del. +	1:110,000	208	145	63	70	Operation: innumerable stones filling entire common bile duct; autopsy: acute necrotizing choledochitis and cholangeitis with liver abscesses
32	62	F	5 wks.	1/21	0	0	..	..	20	.....	.....	340	95	245	28	Operation: stone in common bile duct; chills and fever for weeks
33	28	M	6 days	4/23	++++	0	..	Trace	140	Pr. +	1:14,000	375	170	205	45	Operation: common bile duct obstructed by echinococcus cyst
				4/27	++	0	..	..	...	Del. +	1:77,000	416	140	276	34	
34	59	M	3 wks.	3/13	++	..	..	Trace	200	Pr. +	1:6,000	416	234	182	56	Autopsy: carcinoma of head of pancreas; lymph node and liver metastases; stenosis of common bile duct; chronic cholangeitis and cholangeitic liver abscesses
				3/19	+++	0	..	..	220	.....	.....	350	208	142	59	
				4/ 3	..	..	..	..	250	.....	.....	268	52	216	19	
35	54	M	10 wks.	5/ 5	++	+	+	+	80	Pr. +	1:45,000	415	180	235	43	Common bile duct obstruction due to stone

36	46	F	3 days	12/26	+	..	..	++	15	Del. +	1:90,000	312	234	78	71	Cholecystectomy and removal of stone in common bile duct 5 years ago; typical symptomatology of common bile duct obstruction
37	57	F	10 days	1/14	+	..	..	+	56	Del. +	1:17,000	315	105	210	33	Operation: metastatic carcinoma of liver and hilus lymph nodes
				1/29	+	+	..	..	55	Pr. +	1:14,000	340	104	236	30	
38	52	M	5 days	5/11	+++	++	..	+	40	Del. +	1:33,000	470	228	242	49	Incomplete obstruction of common bile duct by stone or neoplasm; fever and chills throughout course
				5/18	+++	+++	..	+	50	Del. +	1:36,000	326	144	182	44	
				5/23	+++	+++	..	+	30	Del. +	1:100,000	440	208	232	47	
				5/26	0	0	..	+	20	Del. +	1:170,000	357	163	194	46	
				5/29	0	0	..	+++	37	Pr. +	1:65,000	278	98	180	35	
39	69	M	3 days	11/26	+	0	..	+++	75	Pr. +	1:20,000	234	65	169	28	Common bile duct stone with suppurative cholangeitis
				12/ 1	Ft. tr.	Ft. tr.	..	0	25	.....	.....	260	90	170	35	Previous cholecystectomy; recurrent chills, fever and jaundice
				12/26	0	..	..	+++	27	.....	1:80,000	250	90	160	36	Biliary fistula; drainage 600 cc. purulent bile
				1/ 6	+	..	..	..	15	.....	1:200,000	312	110	202	35	Readmission: chills, fever and jaundice; duodenal drainage A and B bile contained pus
				2/28	+	..	..	..	70	.....	1:25,000	125	40	85	32	Readmission: chills, fever, severely ill
40	60	M	.....	2/16	+	+	..	Ft. tr.	95	Pr. +	1:25,000	156	38	118	24	Autopsy: calculi in common bile duct causing occlusion; purulent cholangeitis and cholangeitic liver abscesses; cholemia
41	38	F	.....	3/17	+	0	..	0	75	Del. +	1:25,000	268	150	118	56	Operation: stricture of common bile duct
				3/24	+	0	..	0	65	Pr. +	1:18,000	360	198	162	55	
				3/28	+	0	..	..	80	Pr. +	1:28,000	380	150	230	39	
42	42	M	4 wks.	5/22	+	+	..	..	105	Pr. +	1:30,000	340	208	132	61	Operation: many stones in common bile duct; free biliary drainage
				6/ 8	..	..	..	..	60	Del. +	1:100,000	312	110	202	35	
				6/15	..	..	..	..	30	Del. +	1:100,000	300	85	215	28	
45	72	M	1 wk.	6/23	++	0	..	+	30	Pr. +	1:40,000	312	208	104	67	Obstruction of common bile duct due to carcinoma; aspiration of liver revealed adenocarcinoma cells

hypercholesteremia, so that the relative ratios of total and free to the ester cholesterol were definitely reduced.

Bürger explained this divergency between ester and free cholesterol as due to a stasis of bile containing a disproportionately large percentage of free cholesterol and a relative diminished ester fraction; also as due to a disturbance of fat metabolism caused by a lack of bile in the intestines. Gardner and Gainsborough offer two theories as an explanation for the reduction of ester in some cases of biliary obstruction. First, with the absence of bile from the intestine, no cholesterol is absorbed from the intestine, and as the normally reabsorbed cholesterol is mainly in the ester form, a reduction in the ester content of the blood results exactly as if the patient were on a sterol-free diet. Secondly, the failure of fat resorption is responsible for a diminution in the available supply of fatty acid for conjugation with cholesterol to form the ester. The absence of fat resorption from the intestines also causes the body to deesterize the preformed cholesterol ester in order to utilize the fatty acid. The ester may therefore be relatively, or even absolutely, reduced in obstructive jaundice when the liver becomes damaged as a result of prolonged biliary stasis, superimposed infection, faulty fat metabolism, cachexia. The relative rôle of each factor is often difficult to evaluate.

Thannhauser and Schaber, and Adler and Lemmel consider the lowered ester as evidence of damage to the liver cells occasioned by the stasis. Eppinger, who first described the effects of increased biliary stasis on the intracellular bile ducts, also showed that with continuation of the stasis, more and more liver cells were disrupted, leading to more or less extensive cell necrosis. Schönheimer [35] showed with isolated loops of intestines, in which no connection with the remaining intestine existed, but with intact circulation, that cholesterol is reabsorbed in spite of the absence of bile. In table 1 will be seen data on cases in which the ester fraction of the blood does not depend on the presence or absence of bile in the intestinal tract or on the duration of the jaundice. Moreover, Gardner and Gainsborough admit cases of hypercholesteremia with high esters in spite of persistent failure of fat resorption.

NONOBSTRUCTIVE BILIARY TRACT DISEASE

In the group of cases of nonobstructive biliary tract disease are listed seventeen in which cholecystitis and cholelithiasis were found, without obstruction to the proper outflow of bile. In general, the results, seen in table 2, point to a tendency toward an increased cholesterol content of the blood plasma with normal relationship of the

35. Schönheimer, R., and von Behring, H.: Ztschr. f. physiol. Chem. **192**:102, 1930.

free to ester fractions. This hypercholesteremia can perhaps be considered as expression of a metabolic peculiarity contributing to gallstone formation, especially as the majority of the cases were in females. Rothschild and Wilensky [36] emphasized this relationship in a study of

TABLE 2.—*Nonobstructive Biliary Tract Disease*

			Blood			Cholesterol, Mg. per 100 Cc.				
			Icterus Index	Van den Bergh					Ester, per Cent	
Case	Age	Sex		Direct	Indirect	Total	Ester	Free		Observations
1	66	F	..	.....	.....	125	60	65	48	Operation: chronic cholecystitis; one large stone in gallbladder
2	50	F	..	.....	.....	268	170	98	63	Roentgenogram of gallbladder showed definite stones
3	42	F	..	.....	.....	134	65	69	48	Operation: numerous stones in gallbladder; none in common bile duct
4	34	F	.	Neg.	1:300,000	348	280	68	80	Operation: chronic cholecystitis; no calculi found
5	31	F	..	Neg.	1:500,000	234	108	126	46	Operation: chronic cholecystitis; stones in gallbladder
6	35	F	..	Neg.	1:500,000	180	125	55	69	Operation: chronic and acute cholecystitis; cholelithiasis
7	31	F	..	Neg.	1:500,000	137	106	31	78	Operation: chronic and acute cholecystitis; cholelithiasis
8	27	F	..	Neg.	1:500,000	280	110	170	39	Operation: chronic cholecystitis and cholelithiasis
9	38	F	..	Neg.	1:500,000	268	150	118	56	Operation: chronic cholecystitis; multiple stones in gallbladder and common bile duct
10	32	F	10	Neg.	1:300,000	300	154	146	51	Operation: stones in gallbladder; none in common bile duct
11	37	F	5	Neg.	1:500,000	226	144	82	64	Operation: small stones in gallbladder and cystic duct
12	19	F	..	Neg.	1:500,000	228	125	103	55	Operation: chronic cholecystitis; stones in gallbladder
13	58	F	35	Neg.	1:80,000	175	45	130	26	Operation: stones in gallbladder
						162	85	77	52	Two weeks after operation
14	31	M	8	Neg.	1:330,000	270	104	166	39	Acute cholecystitis; no operation; roentgenogram of gallbladder with dye; no visualization
15	45	F	6	Neg.	1:500,000	340	118	222	35	Operation: chronic cholecystitis and cholelithiasis
16	42	F	5	Neg.	1:500,000	175	88	87	50	Operation: chronic cholecystitis and cholelithiasis
17	67	F	6	Neg.	1:500,000	300	180	120	60	Cholecystitis; roentgenogram of gallbladder; no visualization; improved in short time

the blood cholesterol in cholelithiasis. However, there are several cases with normal or even low cholesterol figures. The latter cannot easily be accounted for, as the usual causes of hypocholesteremia in biliary diseases, such as cachexia, cholemia and superimposed infection, were absent. In general, it will be seen that the changes in the cholesterol

36. Rothschild, M. A., and Wilensky, A. O.: M. Clin. North America **3**:417, 1919.

content of the blood in biliary diseases without obstruction to the outflow of blood are slight and without any particular significance—confirming the previous work of Rothschild and Wilensky,[36] Rothschild and Rosenthal [37] and Campbell.[38]

JAUNDICE DUE TO PARENCHYMATOUS DISEASES OF THE LIVER

A group of thirty-six cases of jaundice due to diffuse parenchymatous disease of the liver was studied; the parenchymatous degeneration ranged in intensity from the mild degree seen in lobar pneumonia, cardiac decompensation and infections to the severest type occurring in fatal cases of acute yellow atrophy. Included are instances of hepatic degeneration due (1) to medicaments, such as arsphenamine preparations, cinchophen and its derivatives, phenobarbital, and (2) to remote diseases such as pneumonia, infections and cardiac decompensations and (3) to primary liver diseases such as so-called catarrhal jaundice, toxic hepatitis, acute, subacute and chronic yellow atrophy. In general, the cases illustrate the importance of a knowledge of the cholesterol picture of the blood plasma in the primary degenerations of the liver and expand the experiences in this field which were recently published.[30]

It will be seen in table 3 that the parallelism between hypercholesteremia and hyperbilirubinemia, seen so commonly in cases of obstructive jaundice, is conspicuously lacking in the cases of severe parenchymatous degeneration of the liver. In the latter the total cholesterol content of the blood plasma is rarely elevated. Usually it is normal or subnormal. In case 20 with a fatal outcome, repeated determinations on 1 cc. of plasma gave total figures too low to be estimated. The hypocholesteremia is seen in cases with very marked jaundice, reaching at times an icterus index of 200 and a bilirubinemia of 1:6,000 by the indirect van den Bergh method. Pronounced reduction in cholesterol affords a means of sharp differentiation between the cases of jaundice due to mechanical obstruction to the outflow of bile and those caused by a primary degenerative lesion of the parenchyma of the liver. This difference, appreciated by Rothschild and Felsen in 1919, has been of service to us in Mount Sinai Hospital as an aid in differential diagnosis. On the contrary, a study of the amount of icterus and the types of bilirubin in the blood has afforded little or no assistance in differential diagnosis. A perusal of tables 1 and 3 will show that the degree of bilirubinemia and types of van den Bergh reactions are similar in the two entirely different conditions, but that in obstructive cases the cholesterol and bilirubin of the blood parallel each other, whereas in the parenchymatous diseases of the liver such an association is lacking. Furthermore, the depression of the total cholesterol in primary hepatic diseases has been used by us

37. Rothschild, M. A., and Rosenthal, N.: Am. J. M. Sc. **152**:394, 1916.
38. Campbell, J. M. H.: Quart. J. Med. **18**:123, 1924

as an aid in prognosis. Cases in which a fairly high amount was found at the onset of the disease had a favorable outcome. Cases with a profound depression below the normal usually ended fatally within a short time.

Observations on the cholesterol esters of the blood plasma were even more striking. In cases 3, 5, 11, 14, 18, 19, 20, 26 and 36, the cholesterol esters were very depressed or even absent during the short, stormy course of the disease. The outcome was fatal, and (except case 3 in which no autopsy was obtained) the postmortem examinations revealed severe parenchymatous degeneration of the liver—marked hepatitis, or acute or subacute yellow atrophy.

In cases 1, 2, 7, 9, 10, 17, 31, 34 and 35—with well marked damage of the liver—the initial cholesterol esters were considerably diminished. With improvement in the condition, the esters gradually rose, both relatively and absolutely, until normal values were obtained with the complete recovery. It will be seen that the ester fraction exactly mirrored the degree of severity of the liver damage, consistently remaining very low or absent in the fatal cases and rising gradually to normal in cases showing clinical evidences of improvement.

In the less severe cases of liver damage—6, 8, 12, 23, 24, 28 and 30—the initial cholesterol esters were lowered, but mainly relatively. This moderate lowering of the esters presaged a good prognosis, which was later confirmed by the subsequent improvement in the condition.

Cases 21, 22, 27, 29, 32 and 33 represent instances of jaundice developing in the course of cardiac insufficiency, with chronic passive congestion of the liver, accompanied in several instances by pulmonary infarctions. The development of jaundice in these cases is due to injury to the liver cells during long-standing passive congestion and anoxemia. A moderate lowering of the esters was present in these cases, and the ester level rose to normal again with improvement.

Of particular interest is the fact that in cases 1, 2, 4, 7, 9, 10, 24, 30 and 31, the total cholesterol and ester figures rose above those found in normal blood plasma concomitant with the clinical improvement and the regression of the evidences of damage to the liver. It is conceivable that occasionally a hypercholesteremia in the stage of healing from acute parenchymatous liver degeneration might be confused with a hypercholesteremia of an incomplete biliary obstruction, but the course of events and the clinical picture should offer easy means of differentiation.

The transition from hypocholesteremia to hypercholesteremia with clinical improvement seems to coincide with regression in the degenerative process and with entry into the regenerative stage. The cholesterol picture mirrors the various stages of the pathologic process and reflects the functional capacity of the diseased organ. Two explanations are

TABLE 3.—*Jaundice Due to Parenchymatous Diseases of the Liver*

Case	Age	Sex	Duration Jaundice Before Admission	Date	Urine		Stool		Blood			Cholesterol, Mg. per 100 Cc.				Observations
					Bile	Urobilin	Bile	Urobilin	Icterus Index	van den Bergh Direct	van den Bergh Indirect	Total	Ester	Free	Ester, per Cent	
1	32	M	6 days	4/ 8	+	+++	..	+	70	.....	.....	150	Trace	150	0	Case of catarrhal jaundice or toxic hepatitis which gradually improved after 5 weeks on a high carbohydrate diet
				4/14	..	..	..	..	...	Pr. +	1:11,000	162	57	105	35	
				4/18	..	..	..	+	120	.....	.....	214	56	158	26	
				4/29	..	..	..	..	75	.....	.....	300	120	180	40	
				5/14	..	..	..	..	20	Del. +	1:330,000	312	188	124	60	
2	25	M	7 wks.	6/26	0	+	..	++	45	Del. +	1:120,000	144	40	104	27	Case of toxic hepatitis; improved after 4 weeks
				6/29	..	..	..	..	35	.....	.....	198	50	148	24	
				7/ 6	..	..	..	..	40	.....	.....	326	80	246	25	
				7/13	..	..	..	..	28	.....	.....	356	156	200	43	
				7/20	..	..	..	..	30	Del. +	1:300,000	312	134	178	43	
3	18	F	3 days	.....	+++	+++	..	..	...	.....	.....	90	0	90	0	Case of acute yellow atrophy of liver: vomiting, bloody and coffee-ground in nature; deepening jaundice; apathy, drowsiness; tyrosine in urine; liver percussed small; coma; death in 3 days
4	47	M	3 days	6/22	0	++	..	+	100	Pr. +	1:17,000	250	98	152	39	Toxic hepatitis due to cinchophen medication
				6/26	++	++	..	+	55	Pr. +	1:50,000	277	90	187	32	
				7/ 9	+	0	..	..	30	Del. +	1:100,000	250	144	106	57	
				7/13	..	..	..	..	38	.....	.....	357	118	239	33	
				7/22	Trace	..	..	+	...	Neg.	1:500,000	340	138	202	40	
5	37	M	.....	2/13	0	++	+	+	...	Neg.	1:300,000	135	Trace	135	0	Autopsy: thrombosis of the branches of the hepatic veins with secondary congestive atrophy of the liver
				2/29	0	+	..	..	60	Pr. +	1:26,000	118	0	118	0	
6	26	M	.....	4/ 6	0	++	..	..	...	.....	.....	200	67	133	34	Acute hepatitis in the course of a lobar pneumonia; jaundice disappeared and patient cured after 5 days
				4/11	0	0	..	..	...	.....	.....	202	156	46	77	
7	20	M	4 days	2/13	++	+	+++	..	120	Pr. +	1:18,000	120	38	82	32	Arsenical toxic hepatitis; improved on high carbohydrate diet
				2/24	0	+	..	..	40	Del. +	1:330,000	290	125	165	43	
				3/ 6	0	0	..	..	...	.....	.....	214	106	108	50	
				3/13	0	0	..	..	...	.....	.....	268	138	130	52	
8	52	M	36 hrs.	12/16	++	+	..	+++	35	Pr. +	1:19,000	238	57	181	24	Acute toxic hepatitis following intravenous saline infusions; improved and discharged after 12 weeks
				12/31	+	++	++	++	30	Pr. +	1:40,000	250	70	180	28	
				2/10	0	0	..	..	...	Neg.	1:500,000	220	170	50	77	
9	40	M	.....	4/ 2	++	++	++	++	75	Pr. +	1:30,000	122	0	122	0	Acute toxic hepatitis following phenobarbital ingestion; improved gradually
				4/ 8	..	++	+	..	35	.....	.....	150	34	116	23	
				4/14	..	++	+	..	25	Neg.	1:330,000	276	134	142	49	
10	31	F	10 days	5/10	+	+	+	+	100	Pr. +	1:12,000	140	0	140	0	Acute toxic hepatitis following cinchophen ingestion; improved gradually
				5/17	+	+	..	..	100	Del. +	1:50,000	154	64	90	42	
				5/26	+	+	+	+	100	Del. +	1:50,000	312	170	142	54	
				6/ 2	..	..	..	..	...			208	125	83	60	
11	52	F	2 wks.	6/24	+	+	+	+	150	Pr. +	1:16,000	130	0	130	0	Autopsy: subacute recurrent yellow atrophy of the liver

12	39	F	2 wks.	7/12	+	++	0	+	70	Pr. +	1:33,000	135	50	85	37	Catarrhal jaundice or toxic hepatitis; patient improved after high carbohydrate and low fat diet
				7/17	+	+++	0	+++	30	.....	.....	162	125	37	77	
				7/24	..	+	..	+	39	.....	.....	190	138	52	72	
13	24	M	2 wks.	7/30	+	+	0	Ft. tr.	200	Pr. +	1:7,000	134	Trace	±134	0	Catarrhal jaundice; went home 11 days after admission against advice
				8/ 4	+	+	..	++	...	.....	.....	188	60	128	32	
14	37	F	3 wks.	10/16	..	..	..	..	...	.....	.....	173	65	108	38	Autopsy: acute yellow atrophy
				10/27	++	+++	..	..	...	Pr. +	1:8,000	104	0	104	0	
15	41	M	.....	.....	++	+	..	..	140	.....	1:50,000	100	36	64	36	Autopsy: lobar pneumonia with parenchymatous degeneration of the liver and marked jaundice
16	38	M	4 days	1/ 5	..	..	..	+	50	.....	.....	200	50	150	25	Lobar pneumonia involving both lungs; cirrhosis of liver; splenomegaly; hepatitis at autopsy
17	26	M	16 days	1/15	+	0	..	..	75	Pr. +	1:40,000	146	Trace	±146	0	Acute toxic hepatitis due to arsphenamine injections
				1/17	0	++	..	..	...	.....	.....	108	Trace	±108	0	
				2/ 3	0	+	..	..	55	Pr. +	1:60,000	228	98	130	42	
18	59	M	1 wk.	1/15	+	0	+	+	...	.....	.....	100	0	100	0	Autopsy: acute yellow atrophy of the liver
				1/19	+	0	..	..	...	.....	.....	50	0	50	0	
19	26	M	3 wks.	5/23	++++	0	..	+	200	Pr. +	1:7,000	140	Trace	±140	0	Autopsy: subacute yellow atrophy of liver with areas of regeneration
				5/26	++++	0	..	..	...	.....	.....	102	0	120	0	
20	12	F	2 mos.	4/13	++	++	..	+	120	Pr. +	1:20,000	58	0	58	0	Autopsy: subacute yellow atrophy of liver with coarse nodular cirrhosis
				4/17	++	++	..	++	160	Pr. +	1:14,000	70	0	70	0	
				4/23	++	+	..	+	120	Pr. +	1:14,000	65	0	65	0	
				5/ 4	+	Trace	..	..	160	Pr. +	1:40,000	Trace	0	Trace	0	
				5/19	+++	+++	..	++	110	.....	.....	Trace	0	Trace	0	
				5/26	+	0	..	..	120	.....	.....	80	0	80	0	
21	42	M	3 wks.	4/14	0	++	..	+++	22	.....	.....	214	60	154	28	Rheumatic cardiovalvular disease with decompensation and jaundice; improved with rest in bed and digitalis
				4/20	0	Trace	..	..	15	Neg.	1:170,000	250	134	116	54	
22	73	F	.....	5/ 5	..	..	..	..	17	.....	.....	192	50	142	26	Autopsy: chronic valvular disease of mitral and aortic valves; hemorrhagic infarct in right lower lobe; chronic passive congestion of liver
23	24	M	2 wks.	9/ 8	..	..	..	+++	60	Del. +	1:22,000	180	40	140	22	Acute toxic hepatitis or catarrhal jaundice; improved in a month
24	29	M	4 wks.	10/30	0	+++	..	..	...	Ft. tr.	1:100,000	234	70	164	30	Syphilis; arsphenamine toxic hepatitis; improved
				11/ 6	0	0	+	..	12	.....	.....	208	134	74	62	
				11/13	0	+	+	..	15	.....	.....	328	102	226	30	
25	29	M	6 days	.....	+++	+++	+	++	160	Dir. +	1:10,000	140	Trace	±140	±0	Toxic hepatitis after neoarsphenamine
26	48	F	6 wks.	.....	++	+	..	0	...	Pr. +	1:12,000	80	0	80	0	Autopsy: chronic hepatitis and cholangeitis with jaundice; hyperplastic thyroid
27	65	M	2 mos.	.....	+++	+++	+	+	120	Pr. +	1:12,000	140	30	110	21	Autopsy: mitral and aortic stenosis and insufficiency; pulmonary infarction; chronic passive liver congestion; jaundice

TABLE 3.—*Jaundice Due to Parenchymatous Diseases of the Liver—Continued*

Case	Age	Sex	Duration Jaundice Before Admission	Date	Urine		Stool		Blood			Cholesterol, Mg. per 100 Cc.				Observations
					Bile	Urobilin	Bile	Urobilin	Icterus Index	van den Bergh Direct	van den Bergh Indirect	Total	Ester	Free	Ester, per Cent	
28	21	M	1 day	.....	+++	++	+	++	60	Pr. +	1:100,000	150	30	120	20	Syphilitic hepatitis; secondary syphilis; after bismuth intramuscularly and mercury inunctions jaundice gradually disappeared
29	38	F	.....	.....	+++	++	..	..	22	Del. +	1:140,000	120	30	90	25	Rheumatic cardiac disease with congestive failure; pulmonary infarcts; ascites; enlarged liver; improved
30	45	F	1 day	3/17	0	++	..	..	50	Pr. +	1:28,000	180	80	100	44	Arsphenamine toxic hepatitis; improved in short time
				3/21	Trace	++	..	..	...	.....	.....	208	98	110	47	
				3/24	Trace	++	..	..	30	Del. +	1:140,000	278	125	153	45	
31	25	M	10 days	5/12	+++	0	0	+	120	Pr. +	1:12,000	234	0	234	0	Following medication, jaundice developed with dark urine and clay stools; liver not palpated; percussed fourth right interspace to costal margin in nipple line
				5/18	+++	++	0	+	...	.....	.....	223	84	139	37	
				5/19	+++	+	0	+	...	.....	.....	174	46	128	26	
				5/26	+++	++	0	+	...	.....	.....	208	40	168	19	
				5/29	+++	+++	0	Very ft. tr.	220	Pr. +	1:6,000	195	45	150	23	Seriously ill with bad hemorrhagic throat infection
				6/ 6	+	++	Trace	+	210	Pr. +	1:11,000	288	163	125	56	5/19–5/27
				6/15	++	+	..	..	180	Pr. +	1:11,000	340	170	170	50	Liver became palpable 1 finger-breadth below costal margin; patient greatly improved
32	21	M	.....	.....	..	++	..	..	36	.....	1:60,000	156	Trace	±156	±0	Rheumatic cardiovascular disease with decompensation and jaundice; pulmonary infarction
33	32	M	.....	4/ 4	..	..	..	..	13	Neg.	1:500,000	220	50	170	23	Triosteal, rheumatic cardiovalvular disease with decompensation; jaundice; liver down to umbilicus, hard, pulsating, tender; rest in bed brought rapid improvement
				4/18	..	..	..	..	...	.....	.....	220	110	110	50	
34	43	M	.....	6/12	0	++	..	..	...	.....	.....	116	Trace	±116	±0	Following injection of arsphenamine fever, vomiting, red urine and diffuse dermatitis developed; no jaundice; acutely ill; liver and spleen palpable; improved on high carbohydrate diet; hepatitis (?) without jaundice
				6/17	..	+	..	..	...	Neg.	1:500,000	220	47	173	21	
				6/30	..	0	..	..	...	.....	.....	200	118	82	59	
35	46	M	5 wks.	10/ 9	++	++	..	+	...	Pr. +	1:12,000	117	38	79	31	Five weeks ago jaundice followed by ascites; repeated paracenteses in hospital
				10/11	+	+	..	+	135	.....	.....	98	33	65	33	
				10/23	++	+++	..	+	...	Pr. +	1:60,000	60	Trace	60	0	Tyrosine in urine
				11/ 6	0	+	..	+	45	Del. +	1:200,000	174	125	49	72	Toxic jaundice with coarse nodular cirrhosis; improved but ascites continued to recur
36	16	F	1 mo.	6/11	+	+	..	++	95	Del. +	1:50,000	150	56	94	37	Autopsy: subacute yellow atrophy; coarse nodular cirrhosis of liver
				7/ 6	+	Very ft. tr.	..	..	90	.....	.....	108	Trace	±108	0	

TABLE 4.—*Atrophic Cirrhosis of the Liver*

Case	Age	Sex	Urine		Stool		Blood			Cholesterol, Mg. per 100 Cc.				Observations
								van den Bergh						
			Bile	Urobilin	Bile	Urobilin	Icterus Index	Direct	Indirect	Total	Ester	Free	Ester, per Cent	
1	39	M	..	..	..	..	..	.....	.....	190	100	90	53	Chronic alcoholism for many years; ascites, hematemesis and melena present three months ago on first admission
			0	+	..	..	10	Neg.	1:500,000	160	108	52	68	
2	61	F	..	..	..	..	8	.....	.....	208	140	68	67	Repeated alcoholic sprees for past five years; enlarged, hard, irregular liver; spleen not palpable
3	64	M	0	+	..	..	..	.....	.....	156	117	39	75	Autopsy: atrophic portal cirrhosis with adenoma
4	40	F	Trace	++	..	..	..	Del. +	1:100,000	195	94	101	48	Long history of alcoholism; jaundice developed following alcoholic spree 6 weeks before admission; liver enlarged; spleen palpable
			Trace	+	..	..	25	.....	.....	210	114	96	54	
5	66	F	..	..	..	..	11	Neg.	1:500,000	208	106	102	51	Autopsy: atrophic cirrhosis of liver; ascites; splenic enlargement; ruptured esophageal varices
6	48	M	0	+++	+	+	45	.....	.....	122	46	75	38	Prominent veins of abdominal wall; ascites; large spleen; subicteric; beginning of impairment of liver function
7	45	M	0	++	..	..	12	Del. +	1:90,000	250	60	190	24	Patient entered with ascites, subicterus; dye, galactose, etc., showed hepatic parenchymatous degeneration in Laennec's cirrhosis; patient improved; no ascites; evidences of collateral cutaneous circulation
			0	+	..	..	10	Neg.	1:500,000	268	108	160	40	
8	33	M	0	++	..	+	7	Neg.	1:500,000	132	70	62	53	Attacks of diarrhea and epistaxis; liver enlarged 2 fingerbreadths below costal margin; edge thin, irregular; spleen markedly enlarged
9	47	M	..	..	..	..	5	Neg.	1:500,000	144	90	54	62	Heavy imbibition of whisky 25 years; liver irregular, tender, 3 fingerbreadths below costal margin; tarry stools; no ascites
10	63	F	..	..	..	..	16	Neg.	1:100,000	150	84	66	56	Autopsy: atrophic cirrhosis of liver with multiple adenoma

offered for the occurrence of a hypercholesteremia in the stage of improvement, viz.: (1) as the regenerative islands of liver tissue have their bile ducts shut off from the rest of the biliary system, an obstructice jaundice occurs with resulting hypercholesteremia, or (2) as the liver functions improve, it is conceivable that only partial functional recovery might occur, with the cholesterol excretion lagging behind the others.

ATROPHIC CIRRHOSIS OF THE LIVER (LAENNEC TYPE)

Ten cases of atrophic cirrhosis of the liver were studied. The process in this type of hepatic disease is slow and drawn out in its evolution, in sharp contrast to the acute parenchymatous diseases of the liver. It will be seen in table 4 that in cases 1, 2, 3, 4, 5, 8, 9 and 10 the values for total cholesterol and ester in the plasma lie within the normal limits. In cases 6 and 7, in which evidences of superimposed liver damage were present, the ester values were subnormal, and in case 7, it rose again as the condition of the patient improved. This normal cholesterol blood picture is in agreement with the work of Adler and Lemmel, who observed deviations in the cholesterol level only when a superimposed hepatitis or state of coma developed in a patient with Laennec's cirrhosis. Low figures for cholesterol and cholesterol ester are as a rule only seen in the terminal stage of the disease.

COMMENT

A study of the blood cholesterol in various forms of hepatic and biliary disease has yielded instructive and important data, which are of assistance in the differentiation between certain types of jaundice and in the prognosis of the various primary liver degenerations.

In forty-three cases of obstruction of the common bile duct by neoplasms, stones, stricture, carcinomatous glands, a hypercholesteremia was usually present which paralleled the bilirubinemia and the degree of obstruction. The hypercholesteremia and hyperbilirubinemia disappear with the removal of the impediment to the biliary outflow, although the hypercholesteremia may persist for a considerable time after the jaundice has cleared up. Both the hypercholesteremia and the hyperbilirubinemia in obstructive jaundice represent a pure regurgitation phenomenon due to the rupture of the bile canaliculi into the lymph and blood channels. In severe cachexia, long-standing jaundice with cholemia, and in infections superimposed in the biliary tract system, the hypercholesteremia often fails to reach levels proportionate to the hyperbilirubinemia, and it may even be absent.

In about one half of the cases, the cholesterol esters rose proportionately with the free cholesterol. In other cases, the ester fraction, although absolutely increased, did not rise sufficiently to maintain the

normal ratio. In eight cases among the forty-three, there was a definite fall of cholesterol ester. This dissociation between total and ester cholesterol probably depends on several factors. Bürger and Habs, and Gardner and Gainsborough ascribed it to a one-sided increase of free cholesterol as a result of stasis of bile cholesterol, which is always free cholesterol, and to faulty fat metabolism incident to absence of bile from the intestines. Thannhauser and Schaber, and Adler and Lemmel considered the ester fall as an expression of liver damage induced by prolonged biliary stasis, superimposed infections and cachexia. That no one factor can explain the phenomenon is illustrated by cases described by Gainsborough and Gardner, as well as by us, in which high cholesterol esters existed in the blood plasma, in spite of prolonged biliary obstruction and faulty fat absorption.

Thirty-six cases of jaundice due to parenchymatous diseases of the liver were studied. In the more severe hepatic degenerations, the total cholesterol content of the blood plasma was below normal, and in the fatal cases, considerably subnormal. Pronounced lowering of the total cholesterol occurred in the gravest cases—a practically normal level in the less severe cases of parenchymatous liver diseases, in spite of a concomitant marked hyperbilirubinemia. This offers a sharp means of differentiation from jaundice due to obstruction of the common bile duct, in which the hypercholesteremia closely parallels the degree of hyperbilirubinemia. In other words, the hyperbilirubinemia and hypercholesteremia are parallel in obstructive jaundice and dissociated in the primary degenerations of the liver. When the dissociation has been very marked, low total cholesterol values with intense jaundice, the outcome has usually been unfavorable.

The cholesterol ester changes are even more striking. The drop in esters has more or less paralleled the severity of the damage to the parenchyma of the liver. In the very acute and severe cases of hepatic degeneration with fatal outcome, the esters were absent at the onset and throughout the duration of the disease. In the moderately severe cases, the esters were considerably lowered, but rose gradually to normal with improvement in the condition. The ester determinations have therefore proved to be not only of diagnostic import in the recognition of parenchymatous damage, but of extreme value in the prognosis of the disease.

In the stage of recovery from liver damage, the figures sometimes rise above normal both for ester and total cholesterol. This change from hypocholesteremia to hypercholesteremia is construed as evidence of transition from predominately destructive to regenerative changes. The hypercholesteremia of regeneration may last for a considerable time.

In seventeen cases of cholecystitis and cholelithiasis with no jaundice and no obstruction of the common bile duct, the total, free and ester cholesterol did not vary significantly from normal, except perhaps for a tendency to a high normal or even slight hypercholesteremia in a few instances.

Ten cases of atrophic cirrhosis of the liver (Laennec type) were studied. The values for cholesterol, both total and ester, were within the normal range, except when an intercurrent hepatitis or liver degeneration was superimposed in the terminal stage of the disease.

SUMMARY

1. Improvement in the accuracy of diagnosis and prognosis of various hepatic and biliary diseases is possible by means of a quantitative study of the blood cholesterol and cholesterol ester—a simple method requiring only 1 cc. of blood plasma and allowing repeated determinations throughout the course of the ailment.

2. In obstructive jaundice, hypercholesteremia is usually encountered. It roughly parallels the degree of obstruction and the bilirubinemia and returns to normal with relief of the obstruction. Exceptions are noted in cases of marked cachexia, cholemia and superimposed infections. The cholesterol esters in mechanical obstruction rise concomitantly with the total cholesterol in about half the cases; in the other instances they remain normal but lag relatively behind the increased free cholesterol.

3. In degenerative diseases of the liver, a pronounced divergence between the bilirubinemia and cholesteremia usually occurs; the more severe the damage to the liver, the greater the tendency to hypocholesteremia. This divergence between the hyperbilirubinemia and the cholesteremia offers a means of differentiation from the cases of mechanical obstruction. In parenchymatous degeneration of the liver, a drop in cholesterol esters parallels the severity of the damage even more accurately. In the rapidly fatal cases the cholesterol esters are very low or absent throughout the course of the disease; in less severe cases, the initial low ester values eventually rise with improvement in the condition.

4. In atrophic cirrhosis of the liver (Laennec), the cholesterol blood pictures remain normal. Variations occur only when hepatitis or degeneration of the liver are superimposed in the terminal stage of the disease.

5. In cholecystitis and cholelithiasis with no obstruction to the biliary outflow, the blood cholesterol figures are normal or insignificantly elevated.

ANEMIA ASSOCIATED WITH BILIARY FISTULA

S. V. BALDERSTON, M.D.
EVANSTON, ILL.

Confronted with a case of severe anemia in an elderly woman, in which there had been a discharge of large quantities of bile through an external fistula more or less continuously for about three years, I naturally thought that it was a terminal condition due to malignancy, especially as the diagnosis of cancer had been made at the time of operative drainage. The question of pernicious anemia arose, however, on account of the complete achlorhydria and the progressive weakness of the patient over a period of several weeks. Liver extract no. 343 and preparations of fresh liver were therefore administered, with apparently no response; in fact, the cell count dropped from 1,360,000 red cells and 4,600 white cells on the patient's admission to the hospital to 1,050,000 red cells and 3,700 white cells twelve days later. Ferrous arsenite had also been given intramuscularly during this period. The total failure of these methods of treatment seemed definitely to confirm the diagnosis of secondary anemia due to cancer of the gallbladder.

An enormous flow of bile from an emaciated patient probably suggested therapy with bile salts on the general principle of a deficiency syndrome. It was somewhat of a surprise when it was found that from the date that the bile salts were added to the previous therapy, the red cells and hemoglobin began steadily to rise, and that the reticulocytes, which under liver therapy alone showed no signs of change, began to show a moderate increase in number. The red cells, which on admission showed marked changes in shape and size, also began to resume their normal contour.

A search through the medical literature revealed surprisingly little exact information on this subject. Pfaff and Balch, of the Harvard Medical School[1] had made careful observations on a woman with a biliary fistula. After the administration of pills of human bile and then pills of ox bile, the patient's weight increased 14 pounds (6,400 Gm.), and she was in excellent health during the ninety-seven day period of observation. Without exception, textbooks on surgery, including those of an earlier period when external biliary fistula was more frequent, and those published up to the present, dismiss the subject of the loss of bile as a matter of little importance to the human organism. This

1. Pfaff and Balch: J. Exper. Med. **2**:49, 1897.

literature was carefully reviewed by Wangensteen,[2] and he concluded by saying, "I have failed to find any reference to injurious effect from prolonged loss of bile to the exterior." In the literature, I found only several vague references to anemia as a sequence to the continued loss of bile.

In contradistinction to this paucity of careful observation in the human being, within the past ten years, physiologists have published a voluminous literature on the results of a series of observations on external biliary fistula in dogs. This experimental work on dogs seems to show that prolonged loss of bile through an external fistula produces a definite anemia which is not due to a digestive disturbance but to a loss of some element discharged with the bile. In comparing the clinical case reported in this paper with these experimental anemias in dogs, one could not but be struck with the marked similarity between the two as to cause, symptoms and the results of treatment.

Seyderheln and Tammann [3] and also Baumann [4] concluded that the anemia found in dogs with external biliary fistula, while temporarily relieved by the feeding of bile salts, was bound up with the vitamin D factor in the circulation.

From their observations on bile fistulas, Whipple and Smith [5] believe that there is a disturbed physiologic condition related to the lack of the normal internal circulation of the bile salts, that bile salts give a strong stimulation to the liver cells, and that this fact has an important relation to the formation of hemoglobin.

REPORT OF CASE

Mrs. M. F., aged 73, was admitted to the Evanston Hospital on July 6, 1930, showing marked prostration, emaciation, flabby parchment-like, ivory-tinted skin, a blood pressure of 88 systolic and 40 diastolic, weakness and apathy. On admission the blood count showed 24 per cent hemoglobin, 1,360,000 red cells and 4,600 white cells. Some of the red cells had markedly pale-stained central areas: there were anisocytoses and poikilocytoses, marked slight polychromatophilia, no nucleated red cells and some stippled red cells.

The patient had been seen in her home in June, 1927, with what appeared to be an obstruction in the biliary system, with nausea, jaundice, etc. The illness was prolonged over several weeks. In a patient, 70 years of age, there was a presumption of malignant condition. During a later attack in August of the same year, the gallbladder was drained at another hospital, and the postoperative diagnosis was cancer of that organ. During the winter of 1928, there had been short periods when the fistulous tract closed, but there had been more or less continuous leakage

2. Wangensteen, Owen H.: Complete External Biliary Fistula, J. A. M. A. **93**:1199 (Oct. 19) 1929.

3. Seyderheln and Tammann: Ztschr. f. d. ges. exper. Med. **68**:539, 1929.

4. Baumann, W.: Ztschr. f. d. ges. exper. Med. **75**:401, 1931.

5. Whipple, G. H., and Smith, H. P.: J. Biol. Chem. **89**:727 (Sept. 30) 1930.

ever since. Examination of the stools sometimes showed traces of bile, but usually it gave negative results. The present attack began with dyspnea on exertion and general weakness, which had been progressive and had extended over several weeks. Urinalysis showed: albumin, 1 plus, and bile, negative; contents of the stomach showed no free hydrochloric acid. The reticulocytes were recorded as 2 in 500 cells. The blood count on July 19 revealed: hemoglobin, 25 per cent; red cells, 1,050,000 and white cells, 3,200 and on August 29: hemoglobin, 68 per cent, red cells, 3,200,000 and white cells, 7,750. The red cells gradually resumed their normal appearance, and the number of reticulocytes increased to 6 per five hundred cells.

Therapy with iron and arsenic was begun on admission; liver therapy was begun on the fourth day. Bile therapy was begun on July 19. After the patient left the hospital, liver therapy was discontinued, and the administration of bile salts was continued, with the addition alternately of iron and arsenic and cod liver oil. The blood picture became entirely normal and continued so. During the summer of 1931, the patient was given bile salts and glutamic acid only, and after a number of weeks during which neither iron nor cod liver oil was given, the blood count showed: 100 per cent hemoglobin, 4,990,000 red cells and 10,400 white cells. Recently, however, it was found necessary to give iron and arsenic.

SUMMARY

After losing bile through an external biliary fistula for three years, an elderly woman presenting symptoms of severe anemia, prostration and achlorhydria, simulating pernicious anemia but not influenced by liver therapy, immediately began to improve on addition of bile salts. At the time of writing, eighteen months after the attack, she is in excellent health. Bile salts and some form of acid therapy have been given for the achlorhydria; other methods of therapy have been employed from time to time, only bile salts and hydrochloric acid being given at times.

The patient has continued to be in good health; the blood has been in an average, normal condition up to the time of writing, and bile salts and hydrochloric or glutamic acid have been given as the only constant therapy.

It is deemed correct to call this case one of secondary anemia due to the continued loss of bile through an external biliary fistula.

CARBOHYDRATE METABOLISM IN A CASE OF HEMOCHROMATOSIS

RICHARD P. STETSON, M.D.
AND
JOHN P. PETERS, M.D.
NEW HAVEN, CONN.

The progressively increasing severity of the diabetes that occurs with hemochromatosis has been recognized since the earliest description of that disease sixty years ago. The symptoms of diabetes have been the complaints that have forced the majority of patients with hemochromatosis to seek medical advice, and before the advent of insulin, diabetic acidosis was the most frequent cause of death in these patients. Since the use of insulin, the peculiarities of the responses to insulin therapy have been repeatedly noted.

In a previous article [1] were reported the clinical and pathologic findings in two cases of hemochromatosis with extensive purpura resembling that of scurvy. One of these (case 2 of the previous report [1]) was observed in the hospital for three hundred and seventy-one days. It is the purpose in this article to prevent and discuss the course of the diabetes in this case.

REPORT OF CASE

A widowed, white, American man, a truck driver, 42 years of age, was admitted to the medical service on May 23, 1928, with a history of swollen, bleeding gums for five months, progressive weakness, pains in the joints and muscles and spreading purpura for six weeks preceding entrance. For at least six months his diet had been wholly lacking in fruit and green vegetables and had been inadequate in all respects. His weight on admission was 123 pounds (55.8 Kg.); there had been a loss of 32 pounds (14.5 Kg.) during the preceding year. There had been no symptoms directly referable to diabetes. At the time of admission, the urine was normal, except for the slightest possible trace of albumin and a trace of urobilin.

In view of the possibility of scurvy suggested by the clinical picture, the patient was given large quantities of orange and lemon juice within twenty-four hours and was subsequently given an antiscorbutic diet liberal in carbohydrates. On such a diet his improvement was rapid.

From the Department of Internal Medicine of Yale University, and the Medical Service of the New Haven Hospital.

1. Stetson, R. P., and Ferris, H. W.: Hemochromatosis and Purpura, Arch. Int. Med., this issue, p. 232.

Glycosuria during the first month of hospitalization was rare and of slight degree. At the end of this period it had definitely increased, and the venous blood sugar during fasting was 139 mg. per hundred cubic centimeters. The patient was given a measured diet consisting of carbohydrate, 150 Gm., protein, 70 Gm., fat, 225 Gm. and calories, 2,900. This abolished the glycosuria, but did not produce a satisfactory gain in weight. The protein and fat were then increased to yield 3,600 calories (table 1, period I). It became necessary to give insulin for the first time ten weeks after admission. Periods II and III demonstrate a progressive impairment of carbohydrate metabolism as measured by increasing glycosuria in spite of rising doses of insulin.

In October (period III), after exhibiting a steady decrease in carbohydrate tolerance for three months, the patient experienced a series of hypoglycemic reactions, occurring usually about midnight. In spite of this, he developed a marked over-night rise in blood sugar concentration, with glycosuria and often slight ketonuria. A division of his evening feeding and insulin between supper and 10 p. m. served to abort the hypoglycemic reactions for a time, but was only moderately successful in clearing the over-night glycosuria.

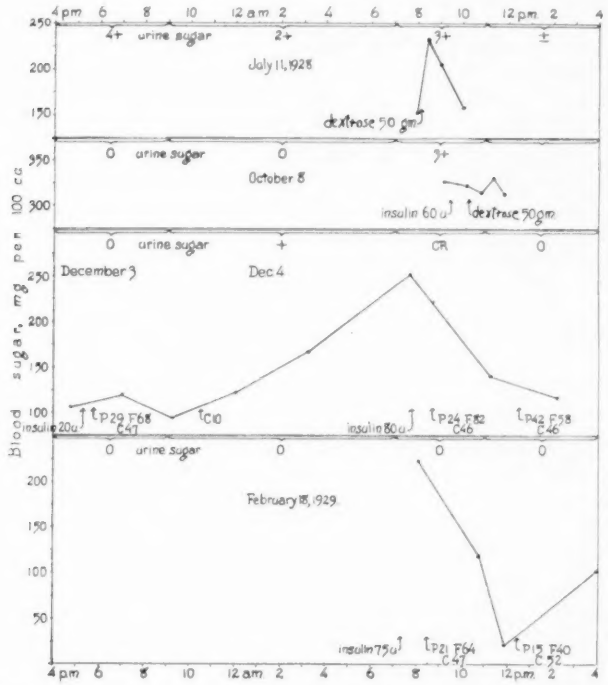
During the next four months (periods IV and V) the carbohydrate tolerance apparently improved. The development of circulatory failure with auricular fibrillation during the last month of observation (period VI) made it difficult to evaluate the diabetic condition during that period. The patient died in coma on May 28, 1929. The concentration of the venous blood sugar three hours before death was 340 mg. per hundred cubic centimeters. The patient did not have diabetic acidosis at the time of death, but presented the terminal picture of hepatic disease.

COMMENT

In the chart are shown blood sugar curves secured at various stages of the disease. Although the four curves are not comparable in all respects, all show the reaction to about 50 Gm. of carbohydrate in the post alimentary period. The first study, made in the early stages of the diabetes when insulin was not required to control glycosuria, represents the hyperglycemic reaction to 50 Gm. of dextrose without insulin. The second, taken later in the disease, represents the reaction to 50 Gm. of dextrose and 60 units of insulin. The third curve, still later, shows the reaction to the regular breakfast, containing about 50 Gm. of carbohydrate, with 80 units of insulin. The fourth curve shows the course of the blood sugar throughout twenty-four hours when the disease was still further advanced,[1] but includes a period comparable to that of the third study.

Between the first and second studies there was a striking increase in the blood sugar concentration during fasting and a diminution of carbohydrate tolerance, evidencing itself in the fact that the second blood sugar curve is far higher than the first, despite the administration of insulin. At the time of the second curve the patient was receiving 60 units of insulin before breakfast and 50 units before supper. In spite of the large evening dose, the blood sugar rose during the night to reach an extremely high level before breakfast. That this rise occurred only during the later hours of the night is indicated by the

facts that sugar did not appear in the urine until after 7 a. m., and that there was a severe reaction to insulin at 2 a. m. of the night following the study of the blood sugar (October 9). The third curve illustrates clearly the over-night rise in blood sugar. By this time it had become necessary to alter the dosage of insulin to 80 units one hour before breakfast and 20 units thirty minutes before supper and to administer 10 Gm. of carbohydrate at 10:30 p. m. to prevent insulin



Cutaneous blood sugar curves at various stages of the disease. The urine sugar was determined by Benedict's qualitative method in specimens of urine divided into four fractions, collected at 7 a. m., 11 a. m., 4 p. m. and 9 p. m. The results of these analyses are shown above each curve. *CR* indicates complete reduction of Benedict's solution; +, *2+*, *3+* and *4+*, various degrees of partial reduction. The administration of insulin and food is represented by the arrows. The nature and quantity of food are represented by the letters, *P* = protein, *F* = fat and *C* = carbohydrate, followed by figures indicating the number of grams of each food given.

shock from occurring during the night. The large morning dose usually enabled the patient to avoid both glycosuria and shock during the day while he was receiving carbohydrate at intervals. At night

a relatively small dose without carbohydrate precipitated shock, although it did not prevent a subsequent rise of blood sugar to a level that initiated glycosuria. As shown in the last curve made, although the blood sugar started at about the same level, a smaller dose of insulin, 75 units, caused a more precipitate fall of blood sugar, ending in shock before lunch. By this time, however, it had become necessary to divide the insulin into three doses: 75 units before breakfast, 10 units before supper and 25 units with 10 Gm. of carbohydrate at midnight. The amount of both the protein and the carbohydrate of the diet were kept practically unchanged throughout the course of the disease; the amount of fat was varied slightly.

The Diabetic Course During the Last Ten Months of Observation

	Diet				Urine*				Blood Sugar, Fasting	Insulin, Daily	Reactions	
					7 a.m. to 9 p.m.		9 p.m. to 7 a.m.		Venous,	Aver-		
Period, 1928	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Wt., Lbs.	Sugar	Acetone	Sugar	Acetone	Mg. per 100 Cc.	age Units	No. in Period	Usual time
I				125								
July-Sept.	80	300	150	134	0-4+	0	0	0	150	0-30	0	
II				134								Mid-
Sept.-Oct.	80	300	150	140	0-2+	0	0-1+	0	260	95	3	night
III				140								
Oct.-Nov.	80	300	150	143	1+-3+	0-2+	4+-0	0-1+	327	120	5	2 a.m.
IV				140								
Dec.-Mar.	80	200	150	143	0-4+	0-1+	0-3+	0-1+	250	100	10	Noon
V				142								
April, 1929	80	200	135	148	0-3+	0-1+	0-4+	0-1+	...	70	1	5 p.m.
VI				148								Irreg-
May	60	170	130	171	0	0	0	0	116	52	3	ular

* The urine sugar was determined by Benedict's test; urine acetone was determined by the nitroprusside test.

The spectacular rapidity with which carbohydrate tolerance deteriorated is shown in the table. The tendency for the blood sugar to rise in the latter part of the night is a well recognized characteristic of severe diabetes and does not distinguish this patient from others without hemochromatosis. The line between glycosuria and shock was, however, peculiarly fine. At times a reaction would occur without a change in diet or insulin; again, an increase of 5 units would precipitate a reaction when there had been profuse glycosuria with the lower dosage. The reactions were sudden in onset, became progressively more severe and were increasingly often associated with paroxysmal auricular fibrillation. Especially in the latter weeks, orange juice given by mouth was not always sufficient to forestall an oncoming reaction. Dextrose given intravenously was always rapidly effective. Other

observers [2] have noted similar fluctuations in carbohydrate tolerance as well as peculiar hypoglycemic reactions in patients with hemochromatosis under insulin therapy.

Callender [2c] has suggested that the loss of available carbohydrate reserve that results from the depletion of hepatic glycogen in advanced disease of the liver is of major importance in the production of the hypoglycemic reactions following the administration of insulin in hemochromatosis. Glycogenesis in the liver is one of the means of disposing of ingested carbohydrate, and the hepatic glycogen thus formed becomes the chief source from which carbohydrate can be rapidly mobilized when needed. Mann and his associates [3] showed that in a dog deprived of both liver and pancreas, greater hyperglycemia develops after the administration of dextrose than in a depancreatized animal, and, at the same time hypoglycemic symptoms develop more rapidly and at higher blood sugar concentrations than in a hepatectomized animal. In hemochromatosis simultaneous advance of the disease in the liver and pancreas should bring about a comparable state.

That the ability to form and store glycogen in the liver was never completely abolished in this patient is suggested by the nocturnal rises in blood sugar in the last three curves in the chart. Even in the last few hours of life the blood sugar remained continuously above 300 mg. per hundred cubic centimeters. It is, however, probable that the glycogen capacity of the liver was unusually small. This would reduce the immediate effectiveness of insulin in disposing of a given dose of carbohydrate, by compelling the organism to rely more completely on the processes of oxidation for its removal, and, at the same time would afford a smaller amount of rapidly available reserve carbohydrate for emergency needs. Nevertheless, when insulin is not acting, continuous,

---

2. (*a*) Allan, F. N., and Constam, G. R.: Insulin Resistance in a Case of Bronze Diabetes, M. Clin. North America **12**:1677, 1929. (*b*) Althausen, T. S., and Kerr, W. J.: Hemochromatosis. A Report of Three Cases with Results of Insulin Therapy in One Case, Endocrinology **11**:377, 1927. (*c*) Callender, G. R.: Hemochromatosis, Internat. Clin. **2**:268, 1928. (*d*) Eusterman, G. B.: Hemochromatosis; Case Report, M. Clin. North America **11**:1376, 1928. (*e*) Hernandez, I. M., and Benaros, M.: Case of Bronze Diabetes, Rev. Soc. de méd. int. y Soc. de tisiol. **6**:1925, 1925. (*f*) Root, H. F.: Insulin Resistance and Bronze Diabetes, New England J. Med. **201**:201, 1929. (*g*) Russell, E.: Hemochromatosis, M. J. Australia **1**:251, 1925. (*h*) Shelton, J. H.: The Iron Content of the Tissues of Hemochromatosis, with Special Reference to the Brain, Quart. J. Med. **21**:123, 1927.

3. Mann, F. C.: Modified Physiological Processes Following Total Removal of the Liver, J. A. M. A. **85**:1472 (Nov. 7) 1925. Mann, F. C.: The Liver in Relation to Carbohydrate Metabolism, Tr. A. Am. Physicians **50**:362, 1925. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Studies of the Physiology of the Liver. XII. Muscle Glycogen Following Total Removal of the Liver, Am. J. Physiol. **74**:238, 1925.

though retarded, processes of neoglycogenesis and glycogenolysis may suffice to produce or maintain a high blood sugar level.

The absence of ketonuria, even with extreme hyperglycemia and minimal dosage of insulin during the comatose terminal condition, is surprising. It is tempting, but hazardous, to connect this also with damage to the liver, which appears to be the organ chiefly concerned in the elaboration of ketone bodies.[4] Wakeman and Morrell [5] found no acetone, by qualitative test, in the urine of starving monkeys in the terminal stages of yellow fever, after prolonged periods of hypoglycemia. The stores of hepatic glycogen of these animals were extremely depleted, removing any obvious source of combustible carbohydrate. That acetonuria develops in Macacus rhesus monkeys when they are deprived of carbohydrate was demonstrated by the subjection of one animal to starvation.

4. Himwich, H. E.; Goldfarb, W., and Weller, A.: The Effect of Various Organs on the Acetone Content of the Blood in Phlorhizin and Pancreatic Diabetes, J. Biol. Chem. **93**:337, 1931.

5. Wakeman, A. M., and Morrell, C. A.: Personal communication.

HEMOCHROMATOSIS AND PURPURA

RICHARD P. STETSON, M.D.
AND
HENRY W. FERRIS, M.D.
NEW HAVEN, CONN.

Since Troisier's [1] description in 1871 of a case of "diabéte sucré" with pigmentary changes, approximately 175 cases of hemochromatosis have been reported. Fourteen, or 9 per cent, of the 153 cases from the literature with data available for study, exhibited some degree of purpura, while in an additional 9 cases, or 6 per cent, hemorrhagic manifestations other than purpura developed in the course of the disease. Other authors have discussed this occurrence and have speculated on its importance in the etiology of the pigment deposits that are characteristic of the disease. In spite of this incidence of purpura in hemochromatosis, it is not generally mentioned as a frequent symptom.

The necropsy records of the department of pathology of the New Haven Hospital between 1917 and 1930 contain reports of 5 cases of hemochromatosis, all of which occurred in males. Two of the patients, at the time of admission, had purpura of such striking degree as to suggest the diagnosis of scurvy. In an earlier case reported from this hospital by Blumer,[2] a petechial eruption developed on the arms and legs a few hours before death.

In this report, the clinical course and pathologic observations in the two more recent cases are presented, together with a discussion of the possible explanations for purpura in hemochromatosis.

REPORTS OF CASES

CASE 1.—J. M., a single, white, Irish-American restaurant worker, 44 years of age, was admitted to the New Haven Hospital on March 21, 1929.

History.—Six months before admission his gums became sore and bled easily, and his teeth loosened. For two weeks he had experienced weakness and had become dyspneic, and a paroxysmal cough and substernal pain had developed. For one week he had raised scanty, bloodstreaked sputum. During this time he had

---

From the Department of Internal Medicine and the Department of Pathology of Yale University and the Medical Service of the New Haven Hospital.

1. Troisier: Diabéte Sucré, Bull. et mém. Soc. anat. de Paris **14**:231, 1871; quoted by McCreery: Canad. M. A. J. **7**:481, 1917.

2. Blumer, G.: Bronzed Diabetes (Hemochromatosis): Report of a Case and Review of the Literature, Proc. Connecticut M. Soc., 1911, p. 190.

noticed reddish "pimples" over his body, which had increased in size to form bluish patches. Seven, and again five days, before admission he had experienced slight epistaxis. His legs below the knees had been swollen for a week.

His dietary history revealed a long-standing deficiency of fruits and vegetables and the fact that for six months he had eaten no meat.

Examination.—He was a well developed, fairly well nourished man, cyanotic and hyperpneic. The lower eyelids were puffy. The gums were swollen and bleeding, with necrosis along their margins. A diffuse papulohemorrhagic rash involved mainly the extensor surfaces of the forearms and, to a lesser extent, the upper parts of the arms and thighs. On the inner aspect of both legs below the knees were extensive purplish areas. A few fading lesions were scattered over the chest and abdomen. Both legs were swollen. In the chest, there were signs of diffuse pneumonia, and the heart was moderately enlarged, without murmurs or friction rub. The systolic blood pressure was 138 mm. of mercury;

TABLE 1.—*Laboratory Findings in Both Cases of Hemochromatosis*

Determination	Case 1 (J. M.)	Case 2 (T. N.)
Red blood corpuscles	3,000,000 per c.mm.	3,100,000 per c.mm.
Hemoglobin (Sahli)	58 per cent	75 per cent
White blood cells	3,250 per c.mm.	6,250 per c.mm.
Neutrophils	72 per cent	59 per cent
Lymphocytes	26 per cent	41 per cent
Blood platelets	100,000 per c.mm.	200,000 per c.mm.
Clotting time	4 minutes, 30 seconds	3 minutes, 45 seconds*
Bleeding time	2 minutes, 30 seconds	3 minutes, 10 seconds†
Blood sugar	103 mg. per 100 cc.	139 mg. per 100 cc.‡
Wassermann reaction of blood	Negative	Negative
Blood culture	No growth	No growth
Liver function test	.....	Slight retention after 30 min.§
Gastric analysis	.....	Normal acidity#
Urine: Albumin	Trace	Slightest possible trace
Sugar	Trace	Negative
Sediment	Occasional white and red blood cells	Negative

* One month later: 3 minutes, 10 seconds.
† One month later: 7 minutes, 10 seconds.
‡ Determination made one month after admission.
§ Intravenous bromsulphalein six weeks after admission.
# Six weeks after admission.

the diastolic, 76 mm. The abdomen was distended. Neither liver nor spleen was felt.

The laboratory findings are recorded in table 1. X-ray pictures of the chest taken on admission showed a diffuse pneumonic process with no evidence of fluid.

Course.—The patient was digitalized. A diet high in vitamin content with orange and tomato juice was attempted, but he took nourishment poorly. On one occasion he vomited material like coffee grounds, which gave a strongly positive result in the guaiac test for blood. On the third day fluid appeared in the right knee joint. The temperature was irregular, between 100 and 103 F. After six days the purpura began to fade and the patient seemed brighter, although generalized subcutaneous edema, bilateral pleural effusion and ascites had developed. By abdominal paracentesis on the eighth day 2,500 cc. of straw-colored fluid was obtained, which yielded no growth on culture. His cyanosis and respiratory difficulty progressed, and he died eight days after admission.

Pathologic Observations.—Necropsy was performed one hour after death by Dr. George C. Wilson. The skin and sclerae were slightly icteric. Numerous dark red spots were scattered over the legs. On the thighs, these were not more than 2 mm. in diameter and usually surrounded the hair follicles, but on the

ankles the hemorrhages were confluent and were from 1 to 5 cm. in diameter. There was pitting edema over the extremities up to the pelvis. There were numerous hemorrhages in the skin of the scrotum. The peritoneal cavity contained fully 2 liters (2,000 cc.) of pale opalescent fluid; the peritoneal surfaces were smooth. In each pleural cavity about 730 cc. of clear fluid was found. A few firm, ribbon-like adhesions bound the pleural surfaces together in the regions of the apexes and bases. The pericardial sac contained about 175 cc. of straw-colored fluid, in which were a few weblike masses of pale brown, semisolid material.

On microscopic examination, the skin showed a small amount of golden-yellow pigment granules, especially in the connective tissue cells adjacent to the sweat glands. The epithelial lining cells of the thyroid and prostate glands were well supplied with hemosiderin. The right knee joint was opened, but contained no blood. The bone marrow from the tibia was yellow, fatty and acellular. The brain and spinal cord were not examined. The important observations in the various other organs are recorded in table 2.

Anatomic Diagnosis.—The primary conditions were: hemochromatosis; gingivitis; anemia; multiple subcutaneous hemorrhages; fibrosis of the heart, liver and pancreas; ascites; hydrothorax; subcutaneous edema; pulmonary atelectasis, and focal pneumonia (bilateral). Subsidiary were fibrous pleural adhesions (bilateral).

CASE 2.—T. N., a 42 year old American truck driver, was admitted to the hospital on May 23, 1928.

History.—About five months before entry he noted swelling and redness of his gums and loosening of his teeth. Six weeks before entry he had a "cold" of three weeks' duration, associated with a series of night sweats and a productive cough. He experienced progressive weakness, pains in the joints and stiffness, especially involving his knees, ankles and shoulders, and observed tiny purplish spots over both shins. These spots increased in number and, for days before entry, a purplish area the size of a silver dollar appeared on the inner aspect of the left knee, which tripled its size within twenty-four hours. Except for a slight transitory remission, the pains in his joint and his weakness progressed to the point of collapse on the evening of admission. He had lost 32 pounds (14.5 Kg.) within a year. For six months his diet had been deficient in fruit and green vegetables. He rarely used alcoholic liquors.

Examination.—He was well developed and moderately emaciated. He complained of pain wherever touched. The hair of the chest, axillae and eyebrows was scanty; the hair of the head was soft and fine in texture. His skin was sallow and of a muddy shade. Petechial hemorrhages were scattered over the body and extremities. On the legs were ecchymoses from a few millimeters to about 5 cm. in diameter, with multiple smaller ones surrounding the hair follicles. One large area of ecchymosis extended from the groin to below the left knee. The left knee and ankle were swollen. The right shin was covered with a raised, hard, red hematoma. There were a few conjunctival petechiae. His gums bled easily and were red and swollen with submucous hemorrhages. Many of his teeth were out, and the remaining ones were loose. There was a slight general adenopathy. The heart and lungs were not remarkable. The systolic blood pressure was 130 mm. of mercury; the diastolic, 80 mm. Generalized tenderness over the upper part of the abdomen extended downward to the umbilicus. The liver was palpable 4 fingerbreadths below the costal margin in the right mammary line. It was hard and tender. The spleen was just palpable on inspiration.

TABLE 2.—*Pathologic Observations in Organs in Both Cases of Hemochromatosis*

Organ	Weight, Gm.		Pigment Deposits (Microscopic)		Fibrosis (Microscopic)		Miscellaneous Observations	
	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2
Heart	410	530	In connective tissue cells; perinuclear in muscle cells	Perinuclear in many muscle cells and in lining cells of capillaries	Focal in left ventricle	Slight	Gross: a few streaks of fat in myocardium. Microscopic: medial coronary coats split; erythrocytes between layers	Gross: right side of heart dilated. Microscopic: many nuclei stain poorly; fat vacuoles in many muscle cells of left ventricle
Lungs	R. 525 L. 550	R. 300 L. 300	In many mononuclear phagocytes scattered in the alveoli	A little in lining cells of mucous glands and in blood vessels	.....	.....	Microscopic: alveolar walls thick; many bronchioles desquamating; small vessels congested	Gross: areas of atelectasis; moderate emphysema
Liver	1,700	2,700	Clumped intracellularly and extracellularly in fibrous tissue and hepatic cell cytoplasm	Much in hepatic cells; less in cells of smaller bile ducts, Kupffer cells and stroma	Marked portal	Marked portal, slight lobular	Gross: thickened, nodular Glisson's capsule, "hobnailed" type	Gross: surface granular. Microscopic: hepatic cells well preserved
Spleen	275	300	In many large mononuclear cells and clumped throughout	In cells of reticulum	.....	Moderate trabecular	Gross: unusually friable	Microscopic: lymphocytes of malpighian corpuscles decreased in number
Pancreas	135	120	Clumped intracellularly and extracellularly in fibrous tissue; granules in acinar cells	Large amounts in acinar cells, less in islet cells	Diffusely increased	Diffusely increased	Gross: individual appearance of islands of Langerhans normal. Microscopic: islands reduced in numbers	Gross: lobular structure distinct
Kidneys	R. 170 L. 200	R. 175 L. 200	Slight, intracellularly and extracellularly in pyramidal epithelium of collecting tubules	Few traces in scattered collecting tubules	Moderate superficial	.....	Microscopic: poorly preserved, convoluted tubule cells disintegrating; blood vessels congested	Microscopic: slight degree of cloudy swelling in tubular epithelium
Suprarenal glands	..	Both 17.5	Masses in outer cortical cells	Slight in superficial cortical cells	Slightly increased			

The laboratory findings are recorded in table 1. X-ray pictures on May 24, June 12 and Sept. 17, 1928, showed no evidence of subperiosteal hemorrhages of the femora, tibiae or fibulae. On June 23, 1928, a roentgenogram of the chest revealed no evidence of pneumonia or of fluid.

Course.—On large amounts of orange juice the patient began to show improvement within forty-eight hours; there was no extension of the purpura and the pains in his joints were less severe. Within three weeks his red blood cell count had increased to 3,900,000 per cubic millimeter and thereafter maintained a level of 4,000,000. During the first month he had two febrile periods of a few days' duration, associated with hyperesthesia of the left upper quadrant and hepatic tenderness. Except for these intervals, his temperature ranged between 98 and 100 F. His purpura gradually disappeared, and he gained strength. He began to show slight glycosuria, which increased in frequency and degree. Four months after admission insulin was started. His diabetic course is discussed in another paper.[3]

Although he gained slowly in weight and strength, his pigmentation increased. On the morning of December 12, one hour after he had apparently recovered from a mild insulin shock, treated with orange juice, he began to have transient auricular fibrillation. Thereafter, in a series of hypoglycemic reactions, he repeatedly exhibited auricular fibrillation, which ceased after the administration of dextrose. Three months later he had an attack typical of coronary occlusion, which lasted about one hour. Within the next week auricular fibrillation became fixed, and edema developed, which was temporarily relieved by digitalization. An x-ray plate of his chest showed the heart to be enlarged in all dimensions.

One month before death a transient crop of petechiae developed on his hands. The edema recurred with bilateral pleural effusion. On May 29, 1929, he died of circulatory and hepatic failure after being in the hospital for a period of three hundred and seventy-one days.

Pathologic Observations.—Necropsy was performed two hours after death. The skin of the chest and abdomen exhibited faint brownish pigmentation. There was slight pigmentation of the skin of the hands. Over the lower extremities from the knees down there was a marked degree of patchy, brown pigmentation, more marked anteriorly. Edema was present in both lower extremities and in the foreskin and scrotum. A yellow, slightly cloudy fluid was found in the peritoneal and both pleural cavities; but, except for adhesions around the spleen and between the apex of the right lung and pleura, the peritoneal and pleural surfaces were smooth. The skin from the chest showed little pigment microscopically, except in a few connective tissue cells about the sweat glands. The thyroid and prostate glands, the testes and many lymph nodes, especially those in the region of the pancreas and abdominal aorta, contained intracellular pigment, which stained with hemotoxylin-eosin and Perl's stains. The stomach was greatly contracted; the mucosa was medium dark brown, and hemosiderin granules were demonstrated in the acidophilic and, to a slight extent, in the other epithelial cells. A slight amount of pigment was found in the endothelial cells of a few small blood vessels of the skin and bone marrow. The bone marrow from the right tibia was yellow, somewhat watery and aplastic. The brain was not examined; there were no changes in the spinal cord. The other pathologic observations are recorded in table 2.

---

3. Stetson, R. P., and Peters, J. P.: The Carbohydrate Metabolism in a Case of Hemochromatosis, Arch. Int. Med., this issue, p. 226.

Anatomic Diagnosis.—The primary conditions were: generalized pigmentation involving particularly the liver, pancreas, spleen and lymph nodes (clinically, bronze diabetes); fibrosis of the liver, spleen and pancreas; ascites; edema of the lower extremities, and hydrothorax (bilateral). Subsidiary were hypertrophy and dilatation of the heart, fibrous adhesions of the pleura (right) and hyaline perisplenitis.

COMMENT ON THE PATHOLOGIC OBSERVATIONS

From the standpoint of pathologic anatomy, these cases differ but little from those described in the literature, except that the cutaneous pigmentation was minimal. In case 2, the pigment in practically every organ gave the blue reaction of hemosiderin with Perl's stain. In the first case, the iron pigment was also widely distributed. The organs involved by the pigmentation and those that showed fibrosis were the organs usually involved in this condition. Although the pancreas in both patients showed a moderate degree of fibrosis, there was no hyalinization of the islands of Langerhans. In the patient in case 1 there seemed to be a slight diminution in the number of these structures. His diabetes was minimal. This lack of correspondence between marked insular change and the clinical picture of diabetes is not unusual. Sheldon,[4] however, noted a correlation between the severity of diabetes in hemochromatosis and the amount of pigment deposited in the pancreas. Our cases suggested a similar correlation.

The necropsy observations that might be correlated with the clinical scorbutic manifestations were slight. In case 1, large and small extravasations of blood were seen in the skin, and the gums were spongy, dark red and receded from the teeth, which were loose. No subperiosteal or joint hemorrhages were found. In this case, the extent of the cutaneous hemorrhage was much greater than that described in the literature in other cases of hemochromatosis. In case 2, the purpura seen on admission disappeared following antiscorbutic treatment and left little evidence of its former presence.

In both necropsies, cultures were made from a number of the organs. As yet, the significance of the isolation of various types of micro-organisms post mortem is not clear, and the possible relation to the clinical picture is difficult to evaluate. In case 1, the general recovery of a hemolytic streptococcus is suggestive of an infection of the blood stream. The elevation of temperature during the patient's last days of life can be explained on this basis. The significance, if any, of the recovery of Bacillus sporogenes from the liver in case 2 is doubtful.

4. Sheldon, J. H.: The Iron Content of the Tissues in Hemochromatosis, with Special Reference to the Brain, Quart. J. Med. **21**:123, 1927.

POSSIBLE FACTORS IN THE PURPURA OF HEMOCHROMATOSIS

Hemorrhagic manifestations other than purpura are mentioned in 6 per cent of the cases of hemochromatosis reported in the literature. Bork,[5] in reviewing a large series of cases of hemochromatosis, found evidence of bleeding in the serous cavities, kidneys and especially the gastro-intestinal tract. Many of these manifestations may be attributed to the effects of portal obstruction.

The importance of the pigmentary cirrhosis of the liver as a factor in the development of the purpuric lesions of hemochromatosis must be recognized. The influence of the liver on coagulation of the blood and production of fibrinogen is great, although even in the presence of extensive damage to the liver there may be little demonstrable change in either of these factors. Nissen,[6] in an analysis of 117 cases of cirrhosis of the liver, did not record the occurrence of purpura; Rolleston[7] mentioned petechiae in cirrhosis, whereas Potter and Milne[8] stated that the hemorrhagic manifestations encountered in hemochromatosis are no more than can be observed in any series of cases of cirrhosis of the liver.

In neither of the cases of hemochromatosis reported here does it seem justifiable to explain the purpura as wholly due to the hepatic damage. Both patients gave a history of definite dietary deficiencies, and in both cases the clinical picture on admission demanded the consideration of scurvy in the differential diagnosis. In case 1, extensive pneumonia and sepsis from a possible infection of the blood stream grafted on cirrhosis of the liver offer an adequate explanation for the development of symptomatic purpura, although the condition of the gums early in the illness and the preexisting dietary deficiency make a scorbutic element likely. Certainly, a definite diminution of this patient's purpura was observed after his ingestion of limited quantities of orange and tomato juice. A mild respiratory infection brought the patient in case 2 into the hospital. His purpura was typically scorbutic and disappeared under antiscorbutic treatment in the face of advancing hepatic insufficiency. This case offers interesting material for speculation that the development of scurvy is enhanced by hemochromatosis.

---

5. Bork, K.: Zur Lehre von der allgemeinen Hämochromatose, Virchows Arch. f. path. Anat. **269**:178, 1928.

6. Nissen, H. A.: Analysis of One Hundred and Seventeen Cases of Cirrhosis of the Liver, M. Clin. North America **4**:555 (Sept.) 1920.

7. Rolleston, H.: Portal Cirrhosis, Oxford Medicine, New York, Oxford University Press, 1921, vol. 3, p. 374.

8. Potter, N. B., and Milne, L. S.: Bronzed Diabetes: Report of a Case, with Special Reference to the Involvement of the Pancreas in Diabetes, Am. J. M. Sc. **143**:46, 1912.

The appearance of scurvy in clinically recognized form has been infrequent in recent years. Minot,[9] discussing the clinical aspects of vitamin deficiencies, suggested that arteriosclerosis may enhance the development of scurvy by damage to the blood vessels, which may prevent the cells from obtaining a suitable supply of active antiscorbutic principle. Mettier, Minot and Townsend,[10] in a recent study of scurvy in adults, stated that "conditions due to vitamin deficiencies and due to lack of certain hormones are brought forth or intensified under various adverse conditions; for example, infectious processes, chronic fatigue, and excesses of various sorts." Deposits of pigment in and around the capillaries produce definite injury to the vascular and perivascular tissues. Not only may this enhance the development of hemorrhagic manifestations by direct injury to the vascular system, but the absorption of protective substances from the blood stream by the tissues may be impaired in a way analogous to that suggested in arteriosclerosis,[9] and susceptibility to scurvy thus be produced.

Diarrhea and other gastro-intestinal complaints have been featured in the symptomatology of many of the reported cases of hemochromatosis. In some, the finding of pigment deposits in the gastro-intestinal tract at postmortem examinations has been noted and discussed. As a result of such deposits, the absorption of antiscorbutic substances from the intestine may be impaired, and this may necessitate, to insure protection against scurvy, the ingestion of larger amounts of potent substances than a normal person would require.

SUMMARY

1. Purpura or hemorrhagic manifestations have been observed in 15 per cent of the 153 cases of hemochromatosis studied in the literature.

2. The clinical and pathologic observations in 2 cases of hemochromatosis with initial symptoms of scurvy are reported, and the pathologic observations are discussed.

3. Possible mechanisms for the development of the hemorrhagic manifestations of hemochromatosis are discussed, and it is suggested that hemochromatosis may predispose the subject to scurvy.

---

9. Minot, G. R.: Some Fundamental Clinical Aspects of Deficiencies, Ann. Int. Med. **3**:216, 1929.

10. Mettier, S. R.; Minot, G. R., and Townsend, W. C.: Scurvy in Adults, Especially Effect of Food Rich in Vitamin C on Blood Formation, J. A. M. A. **95**:1089 (Oct. 11) 1930.

IMPORTANCE OF HEPATOMEGALY AND SPLENOMEGALY IN DIFFERENTIAL DIAGNOSIS

MOSES BARRON, M.D.
AND
A. B. LITMAN, M.D.
MINNEAPOLIS

The liver and the spleen show greater variations in size under abnormal states than any other organs of the body. Livers weighing from two to four times the normal and spleens from five to twenty times the normal are not infrequently encountered. Since these organs are so situated that on enlarging they soon become palpable, definite enlargements become helpful in differential diagnosis. Unfortunately, moderate enlargements are not so helpful in diagnosis, because they are encountered under such a large variety of conditions. However, massive enlargements—splenomegaly and especially hepatomegaly—are caused by relatively few diseases, and the knowledge of this fact will greatly aid in arriving at a correct differential diagnosis by precluding from consideration a large group of diseases that could scarcely be the basis of such enlargement.

In order to establish as accurately as possible the conditions that may give rise to large livers and spleens, the present study was undertaken.

MATERIAL

It consists of the protocols of 12,000 autopsies performed during the past ten years between Jan. 1, 1921, and Jan. 1, 1931 (table 1). It must be understood at the outset that such autopsy material represents a group of cases that does not furnish an accurate cross-section of the sick population of the country or even of the entire local community. Nevertheless, conditions that would not be encountered in this study should be infrequent, since this series represents the autopsies performed at most of the hospitals in Minneapolis, including the University Hospital and the Minneapolis General Hospital, as well as those performed outside these hospitals. Included also are all the coroners' cases and

From the Department of Medicine, University of Minnesota.

Delivered before the Minnesota Academy of Medicine, St. Paul, Minn., Nov. 11, 1931.

The material for this study was obtained in the Department of Pathology of the University of Minnesota, through the permission of Dr. E. T. Bell.

many of the autopsies performed in St. Paul in and outside of the hospitals. The entire mass of material was carefully scrutinized and tabulated as may be seen in tables 2 and 3. Included in these tables are those conditions that produce livers weighing over 2,200 Gm. and spleens weighing over 300 Gm. The basis for this arbitrary choice of figures is the fact that livers and spleens generally become palpable when they reach such proportions. The average normal weight of the adult liver is between 1,500 and 1,900 Gm. and of the adult spleen

TABLE 1.—*Major Causes of Death from Jan. 1, 1921, to Jan. 1, 1931*

Total number of autopsies performed	12,134
Autopsies on infants and children, not reviewed	2,400 (circ.)
Total number reviewed	9,280
Records incomplete	450 (circ.)
Total number listed	7,857
Heart disease	1,582
Malignant tumors	1,083
Accidents	1,042
Pneumonia	808
Tuberculosis (exclusive of cases with amyloidosis)	317
Cerebral hemorrhage (apoplexy)	241
Acute and chronic alcoholism	231

Year	Autopsies	Alcoholism	Per Cent
1921	574	5	0.87
1922	649	13	2.00
1923	849	14	1.70
1924	860	22	2.50
1925	1,061	18	1.70
1926	1,161	33	2.80
1927	1,353	30	2.20
1928	1,736	29	1.70
1929	1,909	35	1.80
1930	1,982	32	1.70

Meningitis	229
Cirrhosis of the liver	129
Nephritis	92
Diabetes	56
Abortion	55
Puerperal sepsis	52
Hodgkin's disease	37
Typhoid fever	24

between 90 and 200 Gm. A biometric statistical study of a larger series of cases is in preparation to determine the range of weights of these organs in different diseases. Curves representing normal weights derived from the study of cases of accidental death from this series are soon to be published by Dr. Edith Boyd, of the Department of Child Welfare of the University of Minnesota. Only adults are included in our study.

INCIDENCE AND DEGREE OF HEPATIC SPLENIC ENLARGEMENTS IN VARIOUS DISEASES

Tables 2 and 3 show the distribution of enlargements of the liver and the spleen among the various diseases and in the different weight

TABLE 2.—*Livers Weighing 2,200 Gm. and Over*

Primary Cause of Death	Total Number of Cases	Cases with Enlargement of Liver		Cases with Enlargement of Liver and Spleen		Cases with Enlargement of Spleen		Hepatic Weight in 100 Gm.; Number of Cases									
		Number	Per Cent	Number	Per Cent	Number	Per Cent	22 to 25	25 to 30	30 to 35	35 to 40	40 to 45	45 to 50	50 to 55	55 to 60	60 to 65	65 to 70	70+
1. Heart disease	1,505*	128	8.5	62	4.1	158	10.4	81	40	7	..	..	..	..	..	..	..	..
2. Tumors	1,083	153	14.1	35	3.2	72	6.7	62	33	21	7	10	5	6	2	4	..	3
A. Carcinoma	990	145	14.6	34	3.4	66	6.6	61	32	21	6	9	4	5	1	3	..	3
(a) Stomach	211	35	16.5	6	2.8	7	3.3	12	4	6	2	4	3	2	..	2	..	..
(b) Pancreas	80	24	30.0	3	3.7	10	12.5	8	7	3	..	2	1	2	..	..	..	1
(c) Colon	72	7	9.7	1	1.3	3	4.1	1	3	1	1	1	..	..	..	..	..	..
(d) Lung	62	11	17.7	3	4.8	5	8.0	4	4	1	..	..	..	..	..	1	..	1
(e) Rectum	53	3	5.6	1	1.8	4	7.5	..	..	1	..	1	..	1	..	..	..	..
(f) Kidney	41	12	29.2	5	12.1	5	12.1	7	3	2	..	..	..	..	..	..	..	..
(g) Breast	49	4	8.1	1	2.04	2	4.08	1	1	1	1	..	..	..	..	..	..	..
(h) Gallbladder and biliary duets	28	8	28.5	1	3.9	4	14.3	4	3	1	..	..	..	..	..	..	..	..
(i) Bladder	40	4	10.0	1	2.5	1	2.5	2	1	1	..	..	..	..	..	..	..	..
(j) Ovary	36	7	19.4	1	2.7	2	5.4	4	3	..	..	..	..	..	..	..	..	..
(k) Testicle	17	3	17.6	1	5.8	2	11.6	2	..	1	..	..	..	..	..	..	..	..
(l) Liver	18	4	22.2	2	11.1	2	11.1	..	2	..	..	1	..	..	1	..	..	..
(m) Uterus	80	3	3.7	..	...	4	5.0	3	..	..	..	..	..	..	..	..	..	..
(n) Prostate	66	3	4.5	2	3.18	3	4.5	3	..	..	..	..	..	..	..	..	..	..
(o) Esophagus	36	1	2.7	1	2.7	1	2.7	1	..	..	..	..	..	..	..	..	..	..
(p) Miscellaneous	101	16	15.8	5	4.9	11	10.9	9	1	3	2	..	..	..	..	..	..	1
B. Melanoma	18	7	38.8	1	5.5	4	22.2	..	1	..	1	1	1	1	1	1	..	..
C. Sarcoma	75	1	1.3	..	...	2	2.6	1	..	..	..	..	..	..	..	..	..	..
3. Pneumonia	808	110	13.6	26	3.2	50	6.1	61	39	8	2	..	..	..	..	..	..	..
4. Miscellaneous acute infections	682	87	12.7	26	3.8	90	13.1	55	26	5	1	..	..	..	..	..	..	..
5. Trauma	613	33	5.3	6	0.99	17	2.7	22	7	3	1	..	..	..	..	..	..	..
6. Fracture of skull	429	31	7.2	1	0.23	7	1.6	21	10	..	..	..	..	..	..	..	..	..
7. Peritonitis	364	24	6.5	7	1.9	24	6.5	18	4	2	..	..	..	..	..	..	..	..
8. Suicide	347	29	8.3	5	1.4	17	4.8	19	7	3	..	..	..	..	..	..	..	..
9. Tuberculosis	318	11	3.4	9	2.8	37	11.3	8	2	..	1	..	..	..	..	..	..	..
10. Cerebral hemorrhage and embolism	241	28	11.6	6	2.4	17	7.05	19	8	..	1	..	..	..	..	..	..	..
11. Meningitis	229	13	5.6	7	3.05	12	5.2	9	3	1	..	..	..	..	..	..	..	..
12. Acute and chronic alcoholism	231	52	22.0	3	1.3	6	2.6	21	16	12	3	..	..	..	..	..	..	..
13. Undetermined	146	6	4.1	1	0.68	8	5.4	5	..	1	..	..	..	..	..	..	..	..
14. Cirrhosis	129	37	28.6	21	16.2	69	34.7	19	13	4	1	..	..	..	..	..	..	..
15. Septicemia	102	18	17.6	10	9.8	32	31.3	12	6	..	..	..	..	..	..	..	..	..
16. Glomerular nephritis	92	4	4.3	1	1.08	8	8.6	3	1	..	..	..	..	..	..	..	..	..
17. Amyloidosis	89	10	11.2	8	9.0	12	13.5	4	2	..	2	..	..	1	1	..	..	..
18. Subacute bacterial endocarditis	87	24	27.5	24	27.5	74	85.05	15	6	3	..	..	..	..	..	..	..	..
19. Pernicious anemia	67	6	8.9	5	7.4	14	20.8	4	1	1	..	..	..	..	..	..	..	..
20. Leukemia	64	30	46.8	29	45.3	49	76.5	9	11	4	4	..	1	..	..	..	..	1
21. Diabetes	56	6	1.07	2	3.5	5	8.9	5	1	..	..	..	..	..	..	..	..	..
22. Abortion	55	6	10.8	6	10.8	9	16.3	4	1	1	..	..	..	..	..	..	..	..
23. Puerperal sepsis	52	12	23.07	9	17.3	21	40.3	7	3	2	..	..	..	..	..	..	..	..
24. Hodgkin's disease	37	6	16.2	6	16.2	23	62.1	3	1	1	..	1	..	..	..	..	..	..
25. Typhoid fever	24	4	16.6	4	16.6	8	33.3	3	1	..	..	..	..	..	..	..	..	..
26. Gumma	7†	4	57.1	2	33.3	4	66.6	1	2	1	..	..	..	..	..	..	..	..

* Exclusive of eighty-seven cases of subacute bacterial endocarditis.
† Exclusive of four cases of congenital syphilis.

* Exclusive of eighty seven cases of subacute bacterial endocarditis.
† Exclusive of four cases of congenital syphilis.

TABLE 3.—*Spleens Weighing 300 Gm. and Over*

Primary Cause of Death	Total Number of Cases	Cases with Enlargement of Spleen		Splenic Weight in Grams; Number of Cases												
		Number	Per Cent	300 to 350	350 to 400	400 to 450	450 to 500	500 to 550	550 to 600	600 to 650	650 to 700	700 to 800	800 to 900	900 to 1,000	1,000 to 1,200	1,200 to 1,400	1,400 to 1,600	1,600 Plus
1. Heart Disease	1,505	158	10.4	76	44	15	10	4	..	4	2	1	1	..	..	..	..	..
2. Tumors	1,083	72	6.7	31	14	11	5	2	2	2	1	1	1	1	1	..	..	..
A. Carcinoma	990	66	6.9	29	14	11	4	2	..	2	..	1	1	1	1	..	..	..
(a) Stomach	211	7	3.3	1	2	2	1	1	..	..	..	..	..	..	..	..	..	..
(b) Pancreas	80	10	12.5	6	4	..	..	..	..	..	..	1	..	..	..	..	..	..
(c) Colon	72	3	4.1	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..
(d) Lung	62	5	8.0	3	..	2	..	..	..	..	..	..	..	..	..	..	..	..
(e) Rectum	53	4	7.5	3	1	..	..	..	..	1	..	..	..	..	..	..	..	..
(f) Kidney	41	5	12.1	2	1	1	..	..	..	..	..	..	..	..	..	..	..	..
(g) Breast	49	2	4.0	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..
(h) Gallbladder and biliary ducts	28	4	14.3	1	..	1	1	1	..	..	..	..	..	..	..	..	..	..
(i) Bladder	40	1	2.5	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..
(j) Ovary	36	2	5.4	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..
(k) Testicle	17	2	11.7	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..
(l) Liver	18	2	11.1	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..
(m) Uterus	80	4	5.0	4	..	..	..	..	..	..	..	..	1	..	..	..	..	..
(n) Prostate	66	3	4.5	..	1	..	1	..	..	..	..	..	..	..	1	..	..	..
(o) Esophagus	36	1	2.7	..	..	..	..	..	..	1	..	..	..	1	..	..	..	..
(p) Miscellaneous	101	11	10.8	4	3	2	..	..	..	..	..	..	..	..	..	..	..	..
B. Melanoma	18	4	22.2	1	..	..	..	..	2	..	1	..	..	..	..	..	..	..
C. Sarcoma	75	2	2.6	1	..	..	1	..	..	..	..	..	..	..	..	..	..	..
3. Pneumonia	808	50	6.1	21	9	9	2	4	1	3	1	..	..	3	..	2	..	..
4. Miscellaneous acute infections	682	90	13.1	36	17	13	12	2	3	1	1	1	..	1	..	..	..	..
5. Trauma	613	17	2.1	7	4	3	..	1	..	..	1	..	..	..	..	..	..	..
6. Fracture of skull	429	7	1.6	4	..	1	1	1	..	..	..	..	..	..	..	..	..	..
7. Peritonitis	364	24	6.5	14	4	2	..	2	1	..	..	1	..	..	..	..	..	..
8. Suicide	347	17	4.8	10	2	3	1	1	..	..	..	..	..	..	..	..	..	..
9. Tuberculosis	317	36	11.3	15	12	5	..	1	2	1	..	..	..	..	..	..	..	..
10. Cerebral hemorrhage and embolism	241	17	7.05	9	4	1	1	1	1	..	..	..	..	..	..	..	..	..
11. Acute and chronic alcoholism	231	6	2.6	4	..	..	2	..	..	..	..	..	..	..	..	..	..	..
12. Meningitis	229	12	5.2	6	4	..	1	1	..	..	..	..	..	..	..	1	..	..
13. Undetermined	146	8	5.4	3	3	..	..	..	1	..	..	..	..	..	..	..	..	..
14. Cirrhosis	129	69	34.7	17	9	8	9	7	5	4	1	2	5	2	..	..	..	..
15. Septicemia	102	32	31.3	16	3	6	3	..	..	1	..	2	..	1	..	..	..	..
16. Glomerular nephritis	92	8	8.6	4	3	..	..	..	..	1	..	1	..	..	1	..	..	1,985
17. Amyloidosis	89	12	13.5	4	2	1	1	..	1	..	..	..	..	..	1	..	..	..
18. Subacute bacterial endocarditis	87	74	85.05	16	11	11	8	8	1	7	2	2	7	..	..	..	..	..
19. Pernicious anemia	67	14	20.8	2	4	5	1	..	..	1	..	..	1	..	..	..	..	11 †
20. Leukemia	64	49	76.5	6	3	3	3	4	2	6	2	1	2	5	7	1	..	..
21. Diabetes	56	5	8.9	3	..	..	1	..	1	..	..	..	..	..	..	..	..	..
22. Abortion	55	9	16.3	1	..	3	2	1	..	..	..	1	1	1	..	..	..	..
23. Puerperal sepsis	52	21	40.3	9	3	4	3	..	..	..	..	1	1	..	..	..	..	..
24. Hodgkin's disease	37	23	62.1	2	2	5	1	3	1	1	1	..	1	4	1	..	1	..
25. Typhoid fever	24	8	33.3	2	..	3	1	1	..	1	..	..	..	..	..	..	..	..
26. Gumma*	7	4	57.1	1	..	..	1	1	..	..	..	..	..	..	1	..	..	..
27. Histoplasmosis	1	1	100.0	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..

* Exclusive of four cases of congenital syphilis.

† 1,620, 1,650, 1,700, 1,950, 2,200, 2,280, 2,400, 2,750, 2,750, 2,860, 3,760.

groups. The weights as recorded are in many instances considerably less than the weights of the organs in the body during life, because of the loss of blood content. It should be observed that this series does not include certain other diseases found in tropical and subtropical countries which may also produce hepatomegaly and splenomegaly, such as malaria, kala-azar, and amebic abscesses of the liver. Still another group of diseases is not present in this list, the absence of which cannot be so readily explained. Not a single case of Gaucher's disease was found, that peculiar, rare disease characterized by "foamy" enlarged cells of the reticulo-endothelial system of the body which may produce spleens weighing as much as 8,000 Gm. There is also a striking absence of congenital hemolytic jaundice and polycythemia vera (Osler's disease, Vaquez' disease), and there is only one case of Banti's disease. In this case, the spleen weighed 780 Gm., but at autopsy there were such

TABLE 4.—*Banti's Splenomegaly (Postoperative Spleens)*

No.	Splenic Weight, Gm.*	Comment‡
Op. 22-36	?	Spleen extended to navel; histologically, Banti's disease
Op. 22-457	?	Histologically, Banti's disease
Op. 22-474	545	In boy 14 years old; histologically, Banti's disease
Op. 22-590	?	Histologically, Banti's disease
Op. 24-82	640	Marked fibrosis of reticulum; histologically, Banti's disease
Op. 25-842	800	Splenomegaly, leukopenia
Op. 28-669	610	Banti's disease, with cirrhosis of liver
Op. 28-799	?	Marked fibrosis
Op. 30-204	1,200	Histologically, Banti's disease; later, blood changes of lymphatic leukemia developed; still later, diagnosis became uncertain.†

* No weights given in half of the cases; none of the spleens very large.
† Last case definitely not Banti's disease.
‡ In group of spleens operated on were included one from a patient who had Gaucher's disease and two from patients who had hemolytic jaundice; the weights of these spleens are not given.

marked perisplenitis and perihepatitis—probably the result of the numerous tappings for ascites—that on account of the marked surface inflammation the case was included in the miscellaneous group. One other case of Banti's disease was not included because there had been a splenectomy performed three years previously, and the weight of the spleen could not be obtained. It is undoubtedly true that many cases clinically diagnosed as Banti's disease are really cases of aleukemia, cirrhosis of the liver, thrombosis of the splenic vein, etc. In order to determine the average weight of Banti's spleens, the records of the spleens operated on were gone over, and the findings are indicated in table 4. The chief characteristic of this disease is the secondary anemia with leukopenia together with an enlarged firm spleen that histologically shows marked fibrosis.

It will be noted from table 2 that enlarged livers weighing less than twice the normal weight are found in such a large variety of conditions that by themselves they prove of little value for differential diagnosis.

It is only when a true hepatomegaly of 4,000 Gm. or over is encountered—a liver that on the average reaches down to the level of the umbilicus—that the enlargement becomes significant. The same holds true for the spleens weighing below 550 Gm. A spleen weighing 600 Gm. is easily palpable, since it usually extends down to about 4 or 5 cm. below the costal margin.

IMPORTANCE OF HEPATIC AND SPLENIC ENLARGEMENTS IN DIAGNOSIS OF VARIOUS DISEASES (COMMENT ON TABLES 2 AND 3)

Heart Disease.—In heart disease, the condition of the liver is of little significance. The enlargement of the liver is only moderate, being the result of acute or chronic passive congestion. The spleen is also only moderately enlarged; in very few cases it reaches a size of from 600 to 900 Gm. The enlargement is due, as in the case of the liver, to

TABLE 5.—*Hepatomegaly*

	Total Number of Cases	Cases in Which Liver Weighed 4,000 Gm. or More*	
		Number	Per Cent
1. Carcinoma	900	25	2.5
(a) Stomach	211	11	5.2
(b) Pancreas	80	6	7.5
(c) Liver	18	2	11.1
(d) Lung	62	2	3.2
(e) Rectum	53	2	3.8
(f) Colon	72	1	1.4
(g) Miscellaneous (vulva)	101	1	1.0
2. Melanoma	18	5	27.0
3. Leukemia	64	2	3.1
4. Amyloidosis	89	2	2.2
5. Hodgkin's disease	37	1	2.7

* Of the thirty-five cases in which the liver weighed more than 4,000 Gm., twenty-five, or 71.4 per cent, were due to metastatic carcinoma; five, or 14.3 per cent, were due to melanoma; two, or 5.7 per cent, were due one to leukemia and one to amyloid, and one, or 2.9 per cent, was due to Hodgkin's disease. Eighty-six per cent were therefore due to carcinoma.

passive congestion with mild replacement fibrosis, the so-called cyanotic induration. Since the cause of these hepatic and splenic enlargements is generally easily recognized, such enlargements offer no difficulties in diagnosis. It might be pointed out, however, that the enlarged liver in this condition means passive congestion from congestive heart failure, and therefore is an important finding to substantiate the diagnosis of cardiac decompensation.

Cancer.—As may be seen from table 5, malignant tumors comprise the principal source for hepatomegaly, producing the enlargement in 86 per cent of the livers weighing 4,000 Gm. and over. It is to be noted that sarcoma is not included in this table because sarcoma produces enlargement neither of the liver nor of the spleen. Melanoma, on the other hand, was responsible not only for the enlargement in some of

the most massive of the livers, but also for the greatest incidence, 39 per cent, of such enlargement; 27 per cent of the livers affected by melanoma weighed over 4,000 Gm. In the matter of metastases, therefore, melanoma resembles carcinoma, and this characteristic lends great support to those authorities who insist that melanoma should be classified as melanocarcinoma and not as melanosarcoma.

Of the carcinomas proper, those of the stomach produced the largest number of hepatomegalies. It will be seen from table 5 that carcinomas of the gastro-intestinal tract and its appendages (pancreas, liver) almost exclusively produce these very large livers. The only exceptions were two carcinomas of the lung, and one carcinoma of the vulva. Tumors of the prostate, uterus and breast practically never produce true hepatomegalies.[1]

A striking feature of hepatic enlargement in some cases of metastatic carcinoma is the rapidity of its development. In case 1, a massive enlargement developed in about a month. In case 2 a huge enlargement occurred in less than three weeks. An explanation for the rapid increase in size was found at the postmortem examination in case 1 (see a later paragraph); large masses of infiltrated lymph nodes surrounding the portal vein were seen to have infiltrated and ruptured into this blood vessel and thus produced miliary metastases throughout the liver. Naturally such a spread would result in very rapid enlargement. In several of our cases the liver enlarged threefold within a period of a few weeks.

Another important fact to remember is that not infrequently carcinomas and especially carcinomas of the liver may cause very high septic temperature similar to that seen in cases of portal thrombosis or hepatic abscess. Case 2 is a striking illustration of this. The fever in this case was so pronounced that we were convinced that the enlargement was on an infectious basis. We were rather disappointed not to find pus after a number of attempted aspirations through puncture. We should, however, have known at the outset that the size of the liver, which extended several fingerbreadths below the umbilicus, practically excluded the possibility of the enlargement being due to an infectious process. In five of the seven cases of hepatic abscesses in the present study (included under the miscellaneous group), the weights ranged between 2,000 and 2,500 Gm.; one liver, owing to amebic abscess, weighed 2,800 Gm.; the seventh case was somewhat complicated in that there was acute pylephlebitis superimposed on a chronic hepatic condition, probably biliary

1. Since writing this paper, a case has come to autopsy in which there was found a very large nodular liver, weighing 4,350 Gm., riddled with cancer nodules, the primary growth of which was in the prostate, whence it had broken through into the bladder. This is the only case encountered of a hepatomegaly from such a primary location. In this case, also, the liver enlarged very rapidly.

cirrhosis. This liver was riddled with abscesses and weighed 3,800 Gm. We are therefore justified in concluding that inflammatory and suppurative conditions in the liver seldom if ever need to be considered when there is definite hepatomegaly present, even when accompanied by high fever.

In striking contrast to the relative frequency of enlargement of the liver in cases of tumors is the almost complete absence of any such enlargement in the spleen. Of over 1,000 cases of malignant growths, only 7, or less than 1 per cent, showed any definite splenic enlargement. In one of these, the increase was due to a tumor metastasis; in another, to extension of an abscess from the colon; in the rest, the enlargement resulted principally through congestion from pressure of the enlarged lymph nodes on the splenic vein. This relative absence of splenic enlargement in malignant conditions is an important fact to remember

In seventy-five cases of sarcoma there was no single occurrence of hepatic enlargement, and in only one case did the spleen reach a weight of 450 Gm. The absence of hepatic enlargement in sarcoma may therefore be used for differential diagnosis from carcinoma.

Acute Infections.—The acute infections—pneumonia, peritonitis, meningitis and typhoid fever—present only moderate enlargements of the liver and spleen. In these instances, the enlargement of the liver is due principally to cloudy swelling; the spleens are enlarged from acute congestion and splenitis. In the case of typhoid fever there is moderate enlargement of both liver and spleen in 16 per cent of the cases and of the spleen alone in 33 per cent (table 6). The miscellaneous acute infections were associated with several rather large spleens, five of which weighed between 900 and 1,400 Gm. These enlargements were due to acute splenitis. The hepatic weights in this group did not go above 3,500 Gm.

Traumatic Conditions.—Fractured skulls and other traumatic conditions and cerebral hemorrhage produce moderate enlargement of both liver and spleen, and this is the result of acute congestion, cloudy swelling and fatty changes. It is very likely that in a considerable number of cases included in the group of accidents the enlargement of the liver was a result of fatty changes due to alcoholism. About the same may be said in the cases of suicides.

Tuberculosis.—This disease presents nothing significant, except that it is the most important cause of amyloidosis. Primary tuberculosis of the spleen may produce a very large organ, but this condition is extremely rare.

Alcoholism.—Acute and chronic alcoholism is responsible for 22 per cent of the enlarged livers. The enlargement is caused principally by fatty changes. The spleen seems practically unaffected. If we may be

permitted to digress, it might be pointed out that the number of cases of acute and chronic alcoholism (table 1) has not been at all reduced by prohibition, but has actually increased. From three such cases in 1919 and two in 1920, there has been a progressive increase to a total of thirty-three cases, or 2.8 per cent of the number of autopsies performed, in 1926.

In the group of undetermined cases there was one case in which the spleen weighed over 1,200 Gm. This was a case of abscess of the abdominal wall. The pathologic condition seemed to be simple acute splenitis.

Cirrhosis of the Liver.—Cirrhosis of the liver is an interesting subject, since the study reveals the fact that contrary to the general belief there is practically no true hepatomegaly in this condition. At autopsy, in about one half of the cases, the livers presented were smaller than

TABLE 6.—*Combined Hepatic and Splenic Enlargement*

Primary Cause of Death	Combined Hepatic and Splenic Enlargement, per Cent	Enlargement of Liver, per Cent	Enlargement of Spleen, per Cent
Leukemia	45.3	46.8	76.5
Gumma	33.3	66.6	57.1
Subacute bacterial endocarditis	27.5	27.5	85.0
Puerperal sepsis	17.3	23.0	40.3
Typhoid fever	16.6	16.6	33.3
Hodgkin's disease	16.2	16.2	62.1
Cirrhosis of liver	16.2	28.6	34.7
Abortion	10.8	12.7	16.3
Septicemia	9.8	17.6	31.3
Amyloidosis	9.0	13.5	11.2
Pernicious anemia	7.4	8.9	20.8
Melanoma	5.5	22.2	38.8

normal, and in the other half the livers were either normal in size or only moderately enlarged. In only 28 per cent, the livers weighed more than 2,200 Gm., and not one weighed more than 3,700 Gm. It is interesting to note that in case 1, in which the liver extended far below the umbilicus, and at autopsy weighed 6,150 Gm., the condition had been diagnosed clinically by excellent men as probable cirrhosis of the liver. The very size of the liver, together with its rapid enlargement, should have at once precluded such a diagnosis. One should remember, however, that in cirrhosis the liver is usually in the atrophic stage when examined at autopsy, and that in most cases it has passed through the stage of considerable enlargement; this enlargement, however, seldom approaches the massive proportions found in cancer. The spleen in this condition shows a greater tendency to enlargement, weighing more than 300 Gm. in 34 per cent of the cases and over 600 Gm. in 11 per cent of the cases (tables 3 and 7). Many cases of splenomegaly erroneously diagnosed Banti's disease are probably due to cirrhosis of the liver.

Septicemia, Puerperal Sepsis and Abortion.—These conditions may be grouped together with reference to enlargement of the liver and

spleen. The liver shows very moderate enlargement, rarely over 3,500 Gm. The spleen shows a more definite enlargement. Occasionally spleens are found weighing over 600 Gm. The enlargement is due to acute splenitis together with congestion. These conditions are summarized in tables 6 and 7. Glomerulonephritis occasionally shows slight enlargement of these organs, but the reason for that is not clear. In one case the spleen weighed over 600 Gm. This case, however, had an associated very severe anemia, the type of which was undetermined.

Amyloidosis.—An important group in this study is that of livers and spleens enlarged as a result of amyloidosis. When there is present a

TABLE 7.—*Splenomegaly*

Cause of Death	Total Number of Cases	Number in Which Spleen Weighed		Diagnostic Importance*
		600 Gm.	1,000 Gm.	
Leukemia	64	35	19	4 plus
Subacute bacterial endocarditis	87	19	1	2 plus
Cirrhosis of liver	129	14	..	2 plus
Hodgkin's disease	37	9	2	3 plus
Heart disease	1,505	8	..	.....
Acute infections	682	8	2	1 plus
Carcinoma	960	6	1	.....
Pneumonia	808	4	..	.....
Septicemia	102	4	..	1 plus
Amyloidosis	89	3	2	2 plus
Abortion	55	3	..	1 plus
Trauma	1,042	2	..	.....
Pernicious anemia	67	2	..	.....
Puerperal sepsis	52	2	..	.....
Melanoma	18	1	..	.....
Tuberculosis†	317	1	..	.....
Gumma of liver	7	1	..	1 plus
Typhoid fever	24	1	..	.....
Peritonitis	364	1	..	.....
Nephritis	92	1	..	.....
Histoplasmosis	1	1	1	.....
Undetermined	146	1	1	.....

* Splenomegaly is of definite importance for diagnosis in leukemia, Hodgkin's disease, amyloidosis, subacute bacterial endocarditis, cirrhosis of the liver and gumma of the liver.
† Exclusive of cases with amyloidosis.

combination of enlargement of spleen and liver and albuminuria, together with a suppurative lesion (tuberculosis, chronic empyema, chronic osteomyelitis) or gumma, amyloid is probably present. Cases 3 illustrates this point. Tables 5, 7 and 8 show that some of the very great enlargements of liver and spleen may be caused by this condition.

Subacute Bacterial Endocarditis.—This condition produces moderate enlargement of liver and spleen, both showing lesions in 27 per cent of the cases, the spleen itself being enlarged in 85 per cent of the cases (table 6). The splenic enlargement is a result of acute splenitis, frequently associated with infarctions. A sudden, sharp pain in the left hypochondrium that persists for some time in a case in which a cardiac condition obtains should strongly suggest subacute bacterial endocarditis, especially if fever is present. There is no type of acute infection that so frequently shows enlargement of the spleen or of both liver and spleen

as this type of endocarditis (table 6). The enlargement of the spleen therefore is an important finding for the diagnosis of this condition.

Pernicious Anemia.—Pernicious anemia produces only slight enlargement of the liver and spleen. The enlargement is due principally to overactivity in the blood pigment metabolism and to increased storage of the blood pigments.

Leukemia.—Leukemia forms the most important group in the enlargement of these organs, especially of the spleen. Under leukemia are included the lymphatic, myelogenous and mixed types, as well as the aleukemic states of these conditions. Lymphatic leukemia is generally associated with enlargement of the peripheral lymph nodes. In a general way, the spleen shows more massive enlargement in myelogenous leukemia than in lymphatic. Except in aleukemic states and the rare

TABLE 8.—*Splenomegaly (1,000 Gm. or More)*

Primary Cause of Death	Cases in Which Spleen Weighed 1,000 Gm. or More		Cases in Which Spleen Weighed 1,400 Gm. or More*	
	Number	Per Cent of Total	Number	Per Cent of Total
Leukemia	19	65.0	11	78.6
Hodgkin's disease	2	7.0	1	7.1
Amyloidosis	2	7.0	1	7.1
Acute infections	2	7.0	..	....
Subacute bacterial endocarditis	1	3.5	..	....
Carcinoma	1	3.5	..	....
Histoplasmosis	1	3.5	1	7.1
Undetermined	1	3.5	..	....
Total number of cases	29		14	

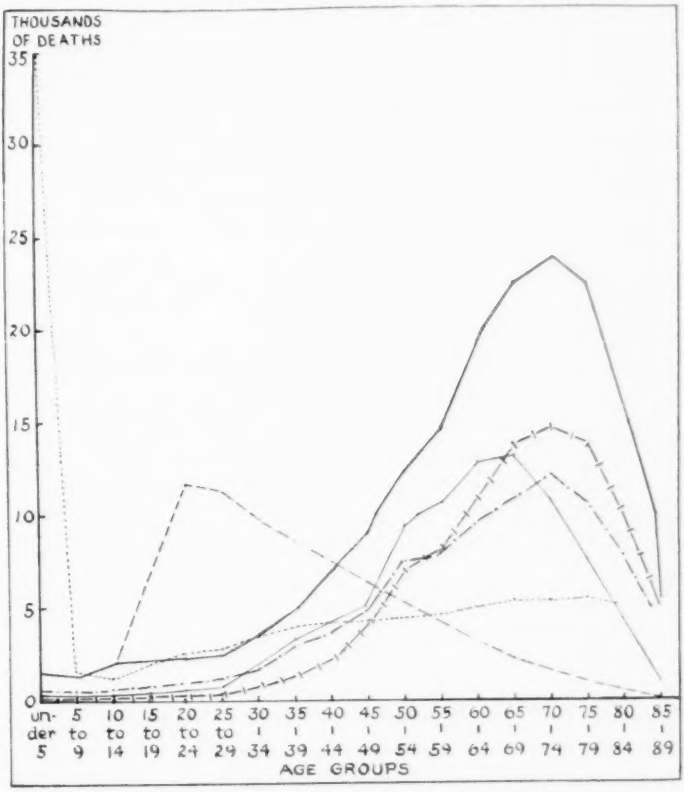
* Seven spleens weighed over 2,000 Gm. each, the largest weighing 3,760 Gm., or more than twice the weight of the normal liver. These were all from patients who had leukemia.

cases of benign lymphadenoses, a definite diagnosis can readily be established by careful examination of the blood. The liver is only moderately enlarged, rarely above 4,000 Gm. In one case, however, it reached the enormous weight of 7,800 Gm. The striking feature of this group of cases is the marked splenomegaly. Of the sixty-four cases, forty-nine, or 76 per cent, showed splenic enlargement, and nineteen, or 30 per cent, of the spleens weighed over 1,000 Gm. (table 8).

In the entire series, seven spleens weighed 2,000 Gm. and over, and in all of these the increase was due to leukemia. The largest spleen weighed 3,760 Gm., or more than twice the weight of a normal liver and about twenty-five times the weight of a normal spleen. Tables 7 and 8 show how leukemia is foremost in causing splenic enlargement, and table 6 shows that it produces also the most frequent combined enlargements.

Diabetes.—Diabetes shows no significant hepatic or splenic enlargement.

Hodgkin's Disease.—This disease forms another interesting group for study. In a total of thirty-seven cases, nine of the spleens weighed over 600 Gm., and two over 1,000 Gm. each. The importance of this disease in splenomegaly is second only to that of leukemia (table 8). The splenic and hepatic enlargements are due to nodular infiltrations



Deaths from heart disease and other principal causes in the United States Registration Area in 1924: heavy solid line, heart disease; light solid line, cancer; dotted line, pneumonia; dash line, tuberculosis; dash-dot line, nephritis; dash-bar line, cerebral hemorrhage.

with the characteristic granulomatous (Hodgkin's) tissue. The liver shows moderate enlargement in some of the cases. Usually this disease presents marked increase in the size of the superficial and deep lymph nodes, a biopsy of which generally establishes the diagnosis. In a few rare cases there are no glandular enlargements, but there develops

an undulant type of fever that is characteristic. In this so-called Pel-Ebstein type of Hodgkin's disease a large spleen can often be palpated.

Gummas.—Gummas are rare, and gummas of the liver are still more infrequent. Only seven cases were found in this series, exclusive of four cases of congenital cirrhosis of the liver. Of the seven cases, four showed hepatic enlargements between 2,200 and 3,500 Gm. The spleen was enlarged in four cases, and in one it weighed over 1,000 Gm. In about one third of the cases, both spleen and liver were enlarged. It is important to remember, therefore, that gumma of the liver is rare and, when present, does not produce massive hepatomegaly.

Histoplasmosis.—There was one unusual case of histoplasmosis in which the spleen was enormously enlarged, weighing 1,450 Gm. Little need be said about this condition, because of its extreme rarity.

GENERAL COMMENT

This statistical analysis of all the cases presenting enlarged livers in our series demonstrates that marked hepatomegaly of 4,000 Gm. or over is present in only a few conditions. This is clearly shown in table 5. By far the greatest number of hepatomegalies encountered were secondary to carcinoma of the stomach, but the greatest percentage from any one condition is from melanoma, which ranks third in actual frequency. This table shows graphically how few are the conditions that can produce true hepatomegaly, and also which conditions should be considered for differential diagnosis whenever a massively enlarged liver presents itself. Usually there is little difficulty in differentiating between Hodgkin's disease, amyloidosis, leukemia, melanoma and carcinoma. When a very large liver is encountered, and the first four conditions can be ruled out, then it is imperative to make a careful study in order to locate the primary site of the carcinoma. Difficulties may arise in determining definitely where the primary lesion is. However, a careful history and physical examination together with roentgen studies should seldom leave one in doubt as to the exact location of the primary tumor.

The number of conditions to be considered in cases of splenomegaly is greater than in those of hepatomegaly. Table 7 shows the relative importance of the spleen in differential diagnosis. According to this table, the spleen is rated in leukemia as four plus, in Hodgkin's disease as three plus, in amyloidosis, cirrhosis of the liver and subacute bacterial endocarditis as two plus, and in gumma, septicemia, abortion and miscellaneous acute infections as one plus. Very massive splenic enlargements, the spleen reaching the pelvic brim, are due almost exclusively to leukemia. Occasionally, however, amyloidosis, Hodgkin's disease and acholuric jaundice may produce very great enlargement of the spleen. An extremely rare condition that may produce a huge splenic increase is

cyst of the spleen. Not a single case was encountered in this series. In our study of reports of autopsies, together with the operative records, true Banti's disease appears to be rare, and the splenic enlargement in this disease in no case was great (table 4). From our observation it would seem that Banti's disease is altogether too frequently diagnosed when an enlarged spleen is present. Gaucher's disease also is to be considered, but in our series not a single case was found. The spleen alone was found to be definitely enlarged in more than 50 per cent of the cases of subacute bacterial endocarditis, leukemia, Hodgkin's disease and gumma. The great frequency of splenic enlargement in subacute bacterial endocarditis is too little appreciated. The presence of combined hepatic and splenic enlargement is valuable for differential diagnosis as shown in table 6. Combined enlargement is most often encountered in leukemia, subacute bacterial endocarditis and gummas of the liver.

TABLE 9.—*Death Rates per Hundred Thousand from Seven Principal Causes of Death in State of New York, Exclusive of New York City, from 1918 to 1926*

Cause of Death	1926	1925	1924	1923	1922	1921	1920	1919	1918
Heart disease	303	273	261	270	260	234	243	221	247
Cerebral hemorrhage	126	120	131	128	132	128	127	123	126
Cancer	121	121	120	117	115	114	109	106	104
Nephritis	121	118	112	111	111	110	117	116	128
Pneumonia	117	98	92	115	109	85	138	129	293
Accidents	86	89	88	90	82	76	78	76	88
Tuberculosis	85	89	91	95	95	99	112	126	145

Table 1 has been brought in only incidentally, as it illustrates some interesting facts, and the following comments, although obviously a digression, are of sufficient interest to warrant inclusion in this paper. It will be noted that heading the list of causes of death is heart disease. This is in accord with statistics as given in table 9 and the chart, general mortality statistics of the State of New York and of the United States Registration Area, respectively. The malignant tumors in our series occupy second place, although in table 9 and the chart they occur in third place. This is probably to be explained by the fact that, because tumors afford greater interest to clinicians, they come to autopsy more frequently. Accidents hold third place in our series, and this figure is astounding. The high mortality from this cause in our series can be explained by the fact that coroners' cases, which are so frequently cases of accidental death, are included in this study. An important lesson to be drawn from this observation is that mortality statistics might be greatly lowered by proper prevention of these accidental deaths, since most of them are preventable.

Pneumonia and tuberculosis appear lower on the list. The figure for tuberculosis is probably a little low owing to the fact that many

patients die in distant sanatoriums, and this precluded postmortem studies by the department of pathology. The importance of acute and chronic alcoholism has already been referred to. There is one item in the list that needs special emphasis, and that is the relative infrequency of true nephritis or glomerulonephritis as a cause of death. It will be noted that deaths from heart disease were more than fifteen times as numerous as those from nephritis. This ratio is probably correct as judged from clinical experience; and the general statistics as shown in table 9 and the chart, where the death rate from nephritis is shown to be as high as from one half to one third of that from heart disease are unquestionably greatly exaggerated. This fact was emphasized by one of us in a previous paper,[2] where it was stated, "The frequency of nephritis is greatly exaggerated because many cases of cardiac decompensation associated with edema and albuminuria secondary to essential hypertension are being diagnosed as nephritis. A correction of this error would greatly lower the nephritic death rate and proportionately increase the death rate from heart disease." It is possible that the statistics on the general mortality from nephritis are four or five times the actual incidence, as no one can doubt the greater accuracy of statistics from postmortem studies as compared with those from the general mortality report. One more item in table 1 is worthy of note, and that is the very low incidence of deaths from typhoid fever. Owing to improved sanitary conditions, especially in regard to water and milk supplies, typhoid fever now ranks among the minor causes of morbidity as well as of mortality.

REPORT OF CASES

CASE 1.—M. T. S., aged 61, was seen in consultation on Nov. 17, 1930. In July, 1930, he had had chills and fever, which lasted two days, and pain in the right side of the chest; the diagnosis was pneumonia. He spat blood several times. On August 9, he was discharged in good condition, but was readmitted on October 8 because of persistent cough and expectoration. A roentgenogram of the chest showed peribronchial infiltration. On October 13, the liver was found enlarged: it increased in size very rapidly and within a month reached to 4 cm. below the umbilicus. On November 17, a diagnosis of primary carcinoma of the lung with metastases to the liver was made. The patient died on November 29. At autopsy, there were a massive tumor in the lower lobe of the right lung and a huge liver showing massive carcinomatous nodules, the organ weighing 6,150 Gm. The peripancreatic and perigastric lymph nodes were markedly infiltrated by the tumor. Histologic sections in the region of the portal veins showed carcinomatous infiltration of the wall of the vein with rupture into the blood stream. This finding explains the massive carcinomatosis of the liver, as well as the rapid enlargement.

CASE 2.—B. W. J., a woman, aged 45, in March, 1930, began to have attacks diagnosed as disease of the gallbladder. Later pain developed in the left lower quadrant of the abdomen. On July 13, fever developed, with marked weakness,

2. Barron, Moses: Cardiac Decompensation and Its Treatment, Minnesota Med. **12**:487, 1929.

nausea and progressive distention of the upper part of the abdomen. When seen on July 25, she presented an enormous liver extending 2 cm. below the umbilicus; the liver had enlarged apparently in two weeks' time. The temperature was septic, with daily variations from 99 to 102.4 F. and over. The blood showed about 50 per cent hemoglobin; leukocytes, 9,000 to 15,000; red blood cells, 3,300,000. The stools showed occult blood. Slight jaundice developed. A diagnosis of probable hepatic abscess or subdiaphragmatic abscess was made. Aspirations gave negative results. On August 5, laparotomy showed massive carcinomatosis of the liver with the primary growth probably in the sigmoid. In this case, the temperature misled the observers in arriving at a correct diagnosis.

CASE 3.—A colored man, aged 33, was admitted to the General Hospital on Aug. 30, 1930, with a history and physical findings of extensive pulmonary tuberculosis of two years' duration. The liver was found to be massively enlarged, extending to below the umbilicus. The urine showed 4 plus albumin; the blood, 38 per cent hemoglobin, 3,600,000 red blood cells and 34,200 white blood cells; the temperature was septic. The large liver puzzled the resident staff. A diagnosis of amyloidosis should have been easy in this case from the history and findings. At autopsy, the liver weighed 5,725 Gm., the spleen 550 Gm., and the kidneys 225 Gm. There was extensive amyloidosis in all these organs.

SUMMARY AND CONCLUSIONS

1. This article presents a critical analysis of the weights of livers and spleens in a series of 12,000 autopsies. Certain tropical splenomegalies and hepatomegalies were obviously not present. A few other splenomegalies, such as those resulting from Gaucher's disease, congenital hemolytic jaundice, polycythemia vera and Banti's disease, were also not encountered.

2. Enlarged livers and spleens—because of their accessibility to direct palpation—occupy a place of great importance in the diagnosis of certain conditions.

3. Ordinarily only a few diseases, carcinoma, melanoma, leukemia, amyloidosis and Hodgkin's disease, produce livers of a size that reaches to the umbilicus (about 4,000 Gm. or over). A differential diagnosis between these conditions can usually be made. It is to be remembered that, in carcinoma, the spleen is seldom enlarged and very rarely is the site of the metastatic tumor.

4. A characteristic feature of some cases of metastatic carcinoma of the liver is the rapidity of the enlargement, which is explained by the rupture of the tumor cells into the portal vein.

5. Some cases of carcinoma of the liver present high septic temperatures.

6. In contrast to carcinoma, sarcoma does not produce enlargement of either liver or spleen.

7. Melanoma resembles carcinoma in producing massive hepatic enlargements.

8. Cirrhosis of the liver, contrary to the general belief, produces no pronounced hepatomegaly. Most cirrhotic livers in our series weighed at autopsy under 2,500 Gm. A moderate enlargement of both liver and spleen is common. The enlarged spleen often erroneously suggests Banti's disease.

9. Gummas of the liver (hepar lobatum) are very rare and produce no marked enlargements. Both liver and spleen are moderately enlarged in about one third of the cases.

10. Enlarged spleens are found in a great variety of conditions, but true splenomegalies occur principally in leukemias, Hodgkin's disease, amyloidosis, cirrhosis of the liver, subacute bacterial endocarditis and acute infections. One must consider also Gaucher's disease, congenital hemolytic jaundice, kala-azar and Banti's disease, although there is a tendency to exaggerate the frequency of the last named. In subacute bacterial endocarditis, the incidence of enlarged spleens is from 75 to 85 per cent, thus showing the great diagnostic importance of an enlarged spleen in this disease. The greatest cause of massive splenomegaly is leukemia.

11. Neither the spleen nor the liver shows any great enlargement in pernicious anemia.

12. Chronic amyloidosis should always be suspected when there is definite enlargement of the liver and the spleen in cases of chronic suppurative processes, especially when albuminuria is present.

13. A proper understanding of the principal causes of splenic and hepatic enlargement is of great assistance in establishing correct diagnoses in a variety of conditions producing enlargement of the liver and spleen.

INFLUENCE ON CARBOHYDRATE METABOLISM OF EXPERIMENTALLY INDUCED HEPATIC CHANGES

III. CHLOROFORM POISONING

T. L. ALTHAUSEN, M.D.

Fellow of the J. Simon Guggenheim Memorial Foundation, from the Department of Medicine, University of California Medical School

SAN FRANCISCO

AND

E. THOENES, Dr.med.

LEIPZIG, GERMANY

Chloroform, according to Mosiman and Whipple,[1] affects mainly the nuclei of hepatic cells. As described by Whipple and Sperry,[2] it produces hyaline necrosis which is of a strictly central distribution, widening out concentrically as the dose of the poison is increased. Chloroform can also produce moderate fatty degeneration in other organs. Occasionally, severe necrosis of the kidney tubules may follow the administration of chloroform, even leading to delayed death of the animal. Williamson and Mann,[3] Opie and Alford,[4] and Mosiman and Whipple all came to the conclusion that the liver is the only organ that is seriously injured by the administration of chloroform.

METHOD

Chloroform was administered subcutaneously in single doses as a 33 per cent solution in oil to fourteen rabbits. Rabbit 739 was given 0.5 cc. of chloroform per kilogram of body weight and rabbit 717, 0.75 cc.; the rest received 1 cc. per kilogram of body weight. The first rabbit was killed on the fifth day. The second animal survived. Of the other twelve rabbits, seven died from forty-eight to sixty hours later, and one died on the seventeenth day after poisoning. The remaining animals recovered. Blood sugar curves for these rabbits were obtained,

From the Medizinische Universitätsklinik, Leipzig, Prof. Dr. Morawitz, Director.

1. Mosiman, R. E., and Whipple, G. H.: Chloroform Poisoning, Bull. Johns Hopkins Hosp. **23**:323 (Nov.) 1912.

2. Whipple, G. H., and Sperry, J. A.: Chloroform Poisoning, Bull. Johns Hopkins Hosp. **20**:278, 1909.

3. Williamson, C. S., and Mann, F. C.: The Hepatic Factor in Chloroform and Phosphorus Poisoning, Am. J. Physiol. **65**:267, 1923.

4. Opie, E. L., and Alford, L. B.: Diet and the Hepatic Lesions of Chloroform, Phosphorus or Alcohol, J. Exper. Med. **21**:1, 1915.

TABLE 1.—*Blood Sugar Curves After the Modified Dextrose Tolerance Test and the Administration of Epinephrine in Rabbits Subjected to Chloroform Poisoning*

Number	Days Since Beginning of Poisoning	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Epinephrine				Average Blood Sugar for 3 Hr. After Dextrose, Water and Insulin	Difference Between Average Blood Sugar for 3 Hr. and Initial Blood Sugar	Average Blood Sugar for 2 Hr. After Administration of Epinephrine	Difference Between Average Blood Sugar for 2 Hr. and 3 Hr.
		Initial Blood Sugar	½ Hr.	1 Hr.	2 Hr.	3 Hr.	3½ Hr.	4 Hr.	4½ Hr.	5 Hr.				
717	Normal	112	155	162	119	83	112	151	194	166	129	+17	145	+62
	2	191	140	184	133	176	184	223	266	281	159	−32	225	+49
	4	108	148	156	169	151	122	148	119	151	159	+51	135	−16
	28	111	140	144	119	94	151	205	209	230	124	+13	182	+88
	2 days after second dose	191	187	180	148	74	126	97	94	101	162	−29	101	+27
	This rabbit had convulsions 1 hour after the beginning of the test and was unconscious with occasional convulsions from the second hour on; it died 30 minutes after completion of the test; liver examined													
739	Normal	126	155	122	112	115	166	144	144	137	123	−3	145	+30
	3	115	112	108	72	90	104	112	140	158	94	−21	120	+30
	Animal killed 4 days later; liver examined													
801	Normal	133	169	162	148	154	178	166	151	152	154	+21	163	+12
	2	137	166	173	180	130	115	144	144	155	164	+27	137	+7
	4	137	126	115	140	119	169	209	184	173	128	−9	177	+58
	6	122	130	140	137	126	140	173	162	151	134	+12	154	+28
	9	122	158	169	137	137	151	169	137	148	148	+26	150	+13
	11	108	140	137	112	119	86	101	94	97	124	+16	98	−21
	13	140	133	126	115	101	158	145	130	142	121	−19	139	+38
	16	155	148	144	115	151	180	191	151	176	137	−18	172	+21
	18	130	144	126	101	97	148	158	158	137	117	−13	146	+49
	23 After dextrose and water	140	137	97	83	83	140	169	140	119	100	−40	138	+55
	27	104	90	65	47	43	115	140	119	101	63	−41	112	+69
	32	151	176	155	148	137	173	166	166	151	153	+2	163	+26
	Second dose of chloroform													
	12 hours	130	155	158	162	151	176	169	158	140	156	+26	162	+11
	36 hours	115	148	140	140	148	86	112	119	130	141	+26	114	−34
	3½ days	133	206	159	108	94	148	177	170	155	136	+3	155	+61
	6½	97	155	151	58	50	112	122	115	130	99	+2	110	+60
	10½	101	97	94	83	86	148	144	126	119	90	−11	130	+44
	The following day, animal was killed for glycogen analysis; liver examined													
804	Normal	158	162	104	104	72	119	154	158	144	126	−32	135	+63
	12 hours	108	122	101	90	86	101	97	108	130	99	−9	101	+15
	36 hours	108	122	126	94	122	108	115	130	119	113	+5	119	−3
	4½ days	108	122	126	112	83	115	162	176	144	112	+4	142	+59
	6½ days	97	119	104	122	108	133	130	112	137	113	+16	125	+17
	8½ days, dextrose and water	113	151	144	137	122	....	....	....	....	137	+24	....	....

	11½	104	94	54	68	126	180	216	209	176	82	−22	189	+63
	13½	108	97	86	83	76	119	144	133	141	107	− 1	126	+50
	15½	104	97	86	72	58	...	68	58	...	80	−24	63	+ 5
	Rabbit was found dead next morning; liver examined													
											102	+ 5	...	....
821	Normal	97	151	119	76	79	...	...	...	...	125	+40	94	+ 4
	24 hours	76	140	144	122	90	94	79	101	115	201	+75	...	....
	4 days, dextrose only	126	173	223	227	180	...	...	...	...	118	+34	...	....
	8	94	133	140	126	68	...	...	...	...	136	+50	...	....
	10	86	133	166	133	122	...	...	...	...	136	+28	...	....
	12	108	158	176	112	115	...	...	...	...	125	+31	...	....
	16	94	137	194	97	83	...	...	...	...	139	+31	...	....
	18	108	216	176	102	97	...	...	...	...	105	−10	...	....
	20	115	149	148	61	76	...	...	...	...				
	Experiment discontinued													
											139	−12	...	....
824	Normal	151	187	158	115	104	...	...	...	...	189	+56	145	−21
	14 hours	133	184	202	202	166	148	169	126	112	204	+103	173	−33
	36 hours	101	148	191	206	206	166	173	170	158				
	Animal found dead on the following morning													
825	2½ days	140	184	187	180	162	184	191	194	191	176	+36	186	+24
	10½ days	173	241	216	148	119	173	220	238	223	178	+ 5	201	+82
	14½ days	97	140	140	83	79	137	169	158	119	107	+10	141	+62
	16½ days	86	112	90	79	83	122	133	137	137	89	+ 3	126	+43
	18½ days	79	79	76	54	61	86	137	130	119	67	−12	111	+50
	21½ days	104	122	140	133	97	119	119	119	119	124	+20	116	+19
	Animal given second dose of chloroform; died 2 days later													
											137	−20	...	....
832	Normal	158	180	169	108	90	...	...	...	...	120	+23	101	−18
	14 hours	97	108	133	122	119	115	94	86	97	68	− 4	78	+46
	8½ days	72	97	133	22	32	76	97	86	72	99	−27	131	+63
	10½ days	126	148	115	72	68	130	148	151	119	105	+ 1	...	....
	13½ days	104	122	130	86	90	...	...	...	...	87	− 7	...	....
	15½ days	94	119	130	61	40	...	...	...	...	129	+32	...	....
	17½ days	97	148	194	104	61	...	...	...	...	131	+48	...	....
	21½ days	83	119	169	122	65	...	...	...	...	100	+ 6	...	....
	23½ days	94	104	137	94	58	...	...	...	...				
	Experiment discontinued													
											118	+10	...	....
835	Normal	108	155	155	104	58	...	...	...	...	144	+61	112	−64
	26 hours	83	94	133	176	176	119	108	94	79				
	Animal died on the following day													

TABLE 2.—*Significant Average Blood Sugar Figures After the Modified Dextrose Tolerance Test and After the Administration of Epinephrine in the Chloroform Poisoned Group* *

Hours After Poisoning	Number of Rabbits	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin						Blood Sugar After 0.1 Mg. of Epinephrine			
		Initial Blood Sugar	Peak of Curve	Difference Between Initial Blood Sugar and Peak	Average Blood Sugar for 3 Hr.	Difference Between Average and Initial Blood Sugar	3 Hr. Blood Sugar	Peak of Curve	Difference Between Peak and 3 Hr. Blood Sugar	Average Blood Sugar After Epinephrine	Difference Between Average Blood Sugar for 2 Hr. and 3 Hr.
12	4	117 (150)	155 (175)	+38 (+25)	141 (139)	+24 (−11)	131 (101)	142	+11	127	−4
12	24	...	...	....	...	....	119 (112)	142 (166)	+23 (+61)	132 (149)	+13 (+37)
24	2	80 (103)	160 (153)	+80 (+50)	135 (110)	+55 (+ 7)	133 (69)	117	−16	103	−30
36	3	108 (147)	160 (173)	+52 (+26)	153 (140)	+45 (− 7)	159 (109)	144	−15	135	−24
36	24	...	...	....	...	....	135 (112)	130 (166)	− 5 (+61)	117 (149)	−18 (+37)

* In parentheses are given normal averages for the same rabbits.

† Animals in which a postepinephrine curve was made before poisoning.

beginning twelve hours after the injection of chloroform and continuing at intervals until the reestablishment of a normal sugar tolerance and a normal response to epinephrine.[5] Data on these experiments are given in detail in table 1. In addition, average figures for the most important stages are shown in table 2.

RESULTS

Acute Stage.—Four rabbits were tested twelve hours after receiving chloroform. The blood sugar at the beginning of the experiment was markedly reduced in all animals. The peak of the curve was at the one hour period in one rabbit and at the two hour period in two rabbits. In all of the animals the three hour blood sugar was much higher than normal and also higher than the initial blood sugar. Finally, the average blood sugar during the three hours was about the same as that taken before poisoning, but the increase over the initial blood sugar was much greater.

The response to the administration of epinephrine was markedly lessened in two rabbits (801 and 804), as testified by a diminished increase of the average blood sugar. In the remaining two animals (824 and 832) a distinct hypoglycemia was observed following the administration of epinephrine.

All of the described abnormalities of sugar metabolism were most pronounced in the rabbit (824) that died two days after poisoning.

Two different rabbits examined twenty-four hours after poisoning exhibited to an even greater extent all the effects of chloroform described for the twelve hour period. In addition the average blood sugar after the administration of dextrose, water and insulin was also absolutely higher than that in the same animals when normal. Our findings were again most marked in a fatal case (835).

The characteristic curves of acute chloroform poisoning were observed in three rabbits also thirty-six hours after the injection of chloroform. The quantitatively most marked abnormalities occurred again in the rabbit that died during the following night.

The Stage of Recovery.—Forty-eight hours after the injection of chloroform, the sugar tolerance and the epinephrine response were still decreased. However, as the first sign of recovery, the initial blood sugar was even higher than normal. On the following two days marked fluctuations of the initial blood sugar were observed. The limits of these fluctuations in the same recovering rabbit (the variation was as great as 94 mg.) were in excess not only of those found in successive tolerance curves of any one normal animal (up to 28 mg.), but of the extremes of all normal animals tested (up to 72 mg.).

5. For description of methods see our first paper: Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes: I. Fasting and Administration of Thyroxine, Arch. Int. Med. **50**:46 (July) 1932.

The peak of the blood sugar curve, the average blood sugar for the three hours and the three hour level also fluctuated considerably after the first two days, but the general tendency was toward normal. After a curve showing normal height and contour was reached, the recovering animals (five) went through a stage in which hypoglycemic curves were observed following the administration of dextrose, water and insulin. In the rabbit (739) that received the smallest dose of chloroform such a hypoglycemic curve was obtained on the fourth day after poisoning. In the other animals it appeared after between ten and eighteen days. An infection of the upper respiratory tract developed in the sixth surviving rabbit (821), and retarded the return of the animal's sugar tolerance to normal until the twentieth day after poisoning, when the investigation was terminated. Of the five rabbits which had shown hypoglycemia during the tolerance test one (739) was killed during this stage; another (804) died sixteen days after the poisoning, and the remaining three later again showed their normal sugar tolerance.

The blood sugar curve after the administration of epinephrine in recovering animals was also subject to wide variations, but normal figures were usually obtained about the fourth day after poisoning. No consistent changes in the blood sugar following injections of epinephrine were seen coincident with the hypoglycemic tolerance curves. The typical stages of chloroform poisoning are exemplified in the blood sugar curves shown in the accompanying chart.

The glycogen content of the liver in one rabbit examined at the time of this peculiar hypoglycemia was 1.2 per cent, whereas that of another animal after the administration of dextrose, water and insulin was 1.07 per cent.

ADDITIONAL EXPERIMENTS

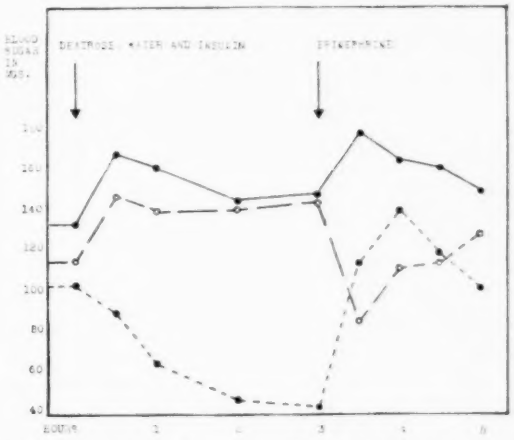
1. *Dextrose Tolerance in Chloroform Poisoning.*—In order to investigate the possibility that some changes observed in the metabolism of carbohydrates under the conditions of the modified dextrose tolerance test might be due to damage of the pancreas, the same test was performed, with the omission of the insulin, in three rabbits at different stages of chloroform poisoning. As will be remembered, in three experiments on two normal rabbits [6] the increase of the average blood sugar over the initial level was approximately doubled when, instead of the standard conditions, dextrose only was given.

When dextrose alone was administered in the usual way to rabbit 821 four days after the poisoning, the increase in the average blood sugar during the three hours was approximately 50 per cent greater than the one observed twenty-four hours after the injection of chloroform, and a little more than double that seen eight days after this event following

6. Descriptions of these experiments are given in the first article (footnote 5).

the tolerance tests with insulin. The same relative increase in the average blood sugar was seen in the second animal (804) after the test without insulin eight days following the administration of chloroform as compared to the modified tolerance test performed six and eleven days, respectively, after poisoning.

A test of dextrose tolerance without insulin was made on the twenty-fourth day on rabbit 801 during the stage when hypoglycemic curves after the administration of dextrose, water and insulin were observed showed that the average blood sugar decreased three times as much as in the usual experiment with insulin performed on the nineteenth day after chloroform had been given. Another experiment with insulin made during the same stage on the twenty-eighth day resulted in the



Typical blood sugar curves after the modified dextrose tolerance test and after the administration of epinephrine in a rabbit (801) at two stages of chloroform poisoning. The solid line represents a curve obtained in the normal state. The irregularly broken line shows the curve thirty-six hours after poisoning. The regularly broken line traces the curve twenty-seven days after administration of chloroform.

same degree of hypoglycemia as the one without insulin on the twenty-fourth day.

2. *Repeated Poisoning With Chloroform.*—Three rabbits that survived the first episode of poisoning were given reinjections with the same dose of chloroform after exhibiting normal curves in our two tests, twenty-one, twenty-eight and thirty-two days, respectively, following the first dose. Two of these animals (717 and 825) died two days after the second injection of chloroform. The third rabbit (801) survived and went through the previously described cycle of changes

relative to sugar tolerance and response to epinephrine, except that the hypoglycemic stage of recovery appeared after ten instead of thirteen days. The animal was then killed for analysis of the liver.

PATHOLOGIC CHANGES

One rabbit that died two days after the first injection of chloroform and one that succumbed in the same length of time after a second injection were examined histologically. In the first (824) all hepatic cells except two or three rows around the portal spaces were necrotic and filled with fat. There was less fat near the portal spaces and in the centers of the necrotic areas. In the second case (717) necrosis involved about three fifths of each hepatic lobule around the central vein. The necrotic cells were full of fat droplets, and there were many wandering cells present.

The livers of three animals that had shown hypoglycemia after the modified dextrose tolerance test were studied histologically. The liver of the rabbit (739) that received the smallest dose of chloroform and was killed four and a half days afterward showed almost complete repair of what had evidently been a moderate injury, with occasional fat droplets.

The animal (804) that died sixteen days after poisoning had a liver that was practically completely restored to normal. Death in this case had nothing to do with the action of chloroform on the liver, but was probably caused, as in one of the rabbits in the series of Opie and Alford,[4] by chloroform necrosis of the kidney tubules.

Finally the rabbit (801) that was killed eleven days after the second dose of chloroform had a liver presenting a normal microscopic picture with a little fat still scattered in spots.

COMMENT

In appraising the effects of a single large dose of chloroform to which about one half of the rabbits succumbed within from forty-eight to sixty hours with advanced central necrosis of the liver, one is struck by the similarity of the functional deficiencies to those produced by phosphorus poisoning, and this notwithstanding the anatomically different localization of lesions produced by these two poisons.

To begin with, the initial blood sugar during the acute stage was markedly lowered in all rabbits. Twelve hours following the administration of chloroform, tolerance to dextrose, as judged by the curve during the first three hours after the test, was greatly diminished. This was indicated by retardation of the peak and prolongation of the period of hyperglycemia. Absolutely, the average blood sugar was about the same as in the normal rabbits, but the relative increase over the initial

level was much greater. At the twenty-four hour and thirty-six hour periods the same abnormalities of the curve were even more pronounced, and in addition the average blood sugar was also absolutely higher than it was previous to the poisoning.

The hyperglycemia due to epinephrine during the acute stage was greatly reduced in half of the animals and replaced by hypoglycemia in the other half.

Forty-eight hours after the administration of chloroform, as the first sign of recovery the initial blood sugar had risen. At later stages considerable fluctuations of the blood sugar level before the tolerance test were observed. Following the first two days the tolerance to dextrose of the rabbits also showed considerable variation, but the trend was toward normal. After normal tolerance was regained, as indicated by the shape of the curve and the average blood sugar, the recovering animals went through a stage of increased sugar utilization. Following this stage, the rabbits again exhibited their normal tolerance.

The response to epinephrine during recovery also varied within wide limits, but the normal degree of hyperglycemia was again found beginning about the fifth day after poisoning.

The glycogen contents of the livers of one rabbit investigated before and of one investigated after the modified dextrose tolerance test were found to be about equally low.

Practically everything discussed in connection with the significance of the changes produced by the administration of phosphorus applies to similar effects of chloroform poisoning. In addition, two features seen only after the administration of chloroform deserve special attention. The first is the protracted character of the hyperglycemia resulting in an unusually high blood sugar at the three hour period. This peculiarity raised anew the question of a possible injury to the pancreas.

In order to arrive at a decision on this point our usual tolerance test with omission of insulin was performed on three rabbits in different stages of chloroform poisoning. The expectation was that without exogenous insulin any considerable pancreatic damage would result in a greater increase of blood sugar, compared with the test that included insulin, than is the case under similar conditions in normal animals. Actually, in the experiments without insulin performed four and eight days after poisoning, the increase of the average blood sugar over the initial value was about 50 per cent greater than the preceding and a little over double that of the following tests with insulin. After allowing for some recovery of the animals during the intervals between tests, we found that the relative increase of the blood sugar was not in excess of that occurring in normal animals. The third tolerance test without insulin performed on the twenty-fourth day during the stage of

increased utilization of sugar showed a much lower curve than the preceding test with insulin which was done before this stage. The curve observed during the same stage after a test with insulin was identical with the one obtained without insulin. After these experiments, the participation of the pancreas in the reduction of the tolerance to sugar produced by chloroform, appears to be ruled out.

The second feature of chloroform poisoning requiring an explanation is the hypoglycemic curve following the test of dextrose tolerance (with or without insulin) which occurs at a certain stage of recovery as shown in the chart. These curves are doubtless an expression of increased utilization of sugar. The arguments in favor of this interpretation are numerous: in the first place, the fact that hypoglycemia begins within thirty minutes of the administration of dextrose, water and insulin; second, the appearance of hypoglycemic curves after sugar tolerance had once returned to normal; third, the fact that after a small dose of chloroform the characteristic low blood sugar was observed earlier, and, finally, the practically complete repair of the liver seen on microscopic examination at this stage, whether it occurred early after a light poisoning or late after a severe one. Observations of the same order, which were interpreted as indicating a period of hyperactivity of the newly formed hepatic cells, were reported by Whipple, Peightal and Clark [7] on an increased phenoltetrachlorphthalein output of the liver following repair after poisoning, and by Whipple and Hurwitz [8] in regard to fibrinogen.

It is certain that hyperactivity on the part of the regenerated hepatic parenchyma plays an important rôle in the increased utilization of sugar by the recovering rabbits. On the other hand, additional factors such as increased activity of the pancreas and of the tissues may also be at work. It seems probable that the compensatory function that the muscles and the pancreas exercise during the period of hepatic insufficiency may materially contribute to the observed hypoglycemia if this compensatory mechanism once established does not recede with the same rapidity as regeneration of the liver progresses. It is of interest that the glycogen content of the liver at this stage of recovery is still very low.

Three rabbits were given reinjections of the same dose of chloroform after recovery. Two of these animals (717 and 825) were dead forty-eight hours later. The third animal (801) lived and went through the

7. Whipple, G. H.; Peightal, T. C., and Clark, A. H.: Tests for Hepatic Function and Disease Under Experimental Conditions; Phenoltetrachlorphthalein, Bull. Johns Hopkins Hosp. **24**:343 (Nov.) 1913.

8. Whipple, G. H., and Hurwitz, S. H.: Fibrinogen of the Blood as Influenced by the Liver Necrosis of Chloroform Poisoning, J. Exper. Med. **13**:136, 1911.

stage of increased utilization of sugar earlier than the first time. While the number of experiments is too small for any conclusions, it may be pointed out that the results are in agreement with the opinion of Wells [9] that a previous injury to the liver predisposes to subsequent chloroform injuries. We have already had occasion to mention the finding by Davis and Whipple [10] of increased tolerance to chloroform in dogs immediately after recovery from the first dose. It is probable that in regard to the question of susceptibility of the liver to repeated doses of hepatic poisons the time that has elapsed since the administration of the preceding dose is an important factor. Our third case seems to indicate that when the action of the second dose of chloroform is not lethal, regeneration of the hepatic parenchyma takes place more promptly.

The Modified Dextrose Tolerance Test in Man in the Light of Experimental Findings.—One of the main difficulties in reproducing in animals by a more or less acute toxic injury pathologic functional states found in certain diseases of the liver in man lies in the condensed nature of the obtained experimental findings. Functional stages that in patients last for weeks, months or years are limited in such animals to days or even hours and may easily be overlooked. Such an example is furnished by the difficulties of interpreting the blood sugar curves of rabbits that received a single large dose of phosphorus. When the results of the more chronic experiments are used as a key, the significance of these curves becomes apparent. If the attempt to reproduce in rabbits abnormalities in the regulation of sugar metabolism observed in human patients with hepatic disease has been at all successful, it is due to the fact that one of the cardinal functions of the liver is involved.

The majority of abnormal blood sugar curves following the modified dextrose tolerance test obtained on patients suffering from diseases of the liver show an initial hyperglycemia which often exceeds that of normal persons, and which before the end of the test drops to a marked hypoglycemia. The same features, namely curves showing reduced tolerance to dextrose followed by a fall in blood sugar, were most clearly observed in rabbits subjected to chronic phosphorus poisoning. In animals that had received large single doses of phosphorus and chloroform the same abnormalities could be identified, but because of the rapid succession of various stages of acute hepatic insufficiency their presence was not so striking.

9. Wells, H. G.: Chloroform Necrosis of the Liver, Arch. Int. Med. **1**:589 (July) 1908.

10. Davis, N. C., and Whipple, G. H.: The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia, Arch. Int. Med. **23**:612 (May) 1919.

The second type of abnormal curve seen in human cases which is characterized by a continuous fall of the blood sugar level finds its counterpart in the hypoglycemic curves obtained during the period of recovery from the effects of chloroform. Since curves of this kind were found largely in subacute yellow atrophy of the liver, alcoholism with suspected beginning cirrhosis [11] and late stages of catarrhal icterus, it seems logical to attribute to them the same significance, namely, temporary hyperactivity associated with regeneration of the hepatic parenchyma.

Occasionally, hypoglycemic blood sugar curves of the second type were encountered in advanced cases of cirrhosis with ascites, etc. In such patients the early hypoglycemia could hardly be taken for a sign of active regeneration of the liver, but probably is comparable to the very low blood sugar curves seen in two of our rabbits (803 and 833) a few hours before death.

SUMMARY

Rabbits receiving one large dose of chloroform were subjected at intervals to a modification of the dextrose tolerance test followed by an injection of epinephrine. Blood sugar curves following these procedures and determinations of the hepatic glycogen before and after the modified dextrose tolerance test were made.

In the acute stage of chloroform poisoning the blood sugar level was reduced in all animals. At the same time there was diminution of the tolerance to sugar, explained at least in part by lack of deposition of glycogen in the liver following the administration of dextrose, water and insulin. Hyperglycemia due to epinephrine was greatly reduced in some animals and replaced by hypoglycemia in others.

During the stage of recovery, the blood sugar level, the sugar tolerance and the response to epinephrine returned to normal. In addition, these rabbits went through a period of increased utilization of dextrose.

It was established that pancreatic lesions played no important part in the observed abnormalities of carbohydrate metabolism.

An attempt was made to correlate the different blood sugar curves after the modified dextrose tolerance test in man with those of animals in various stages of hepatic insufficiency due to phosphorus and chloroform poisoning.

---

11. These patients were subjected to the test some time after the withdrawal of alcohol.

TREATMENT OF LOBAR PNEUMONIA WITH CARBON DIOXIDE AND OXYGEN

REPORT OF TWENTY-SEVEN CASES

J. FLETCHER HANSON, M.D.
AND
ABNER W. CALHOUN, M.D.
ATLANTA, GA.

Pneumonia has challenged man's therapeutic skill for centuries. Hippocrates and other members of the Greek school recognized the disease with its high mortality. Though progress has been made in the knowledge of the clinical features, morbid anatomy and bacteriology of the disease, the death rate remains essentially unchanged, and pneumonia is still one of the most widespread and fatal of all acute diseases.

Various forms of therapy have been heralded, each with claims of reduction in mortality. Chemotherapy, with the use of ethylhydrocupreine and of mercurochrome-220 soluble, has been tried. Vaccines have been used extensively. The greatest therapeutic triumph in pneumonia has been the development of specific immunizing serum. The work of Cole and Moore [1] in developing a specific serum for pneumococci of type I and that of Felton [2] in producing a concentrated serum for pneumococci of types I and II have added to the progress of medicine. One of the most recent forms of therapy suggested for pneumonia is the inhalation of carbon dioxide and oxygen. In this paper a brief review is made of the rationale of its use, and a report is given of twenty-seven patients treated by this method.

Carbon dioxide may be used to stimulate the respiratory center, as was demonstrated by Henderson and Haggard [3] in 1920. These authors used carbon dioxide to eliminate carbon monoxide from the blood of dogs after dangerous degrees of asphyxiation. A year later, in reporting their work on carbon monoxide asphyxia to the American

---

Read before The Southern Interurban Clinical Club, March 19, 1932.

From the Department of Medicine, Emory University Medical School, and the Emory Division of Grady Hospital.

1. Cole, Rufus, and Moore, H. F.: The Production of Antipneumococcic Serum, J. Exper. Med. **26**:537, 1917.

2. Felton, L. D.: A Study of the Isolation and Concentration of the Specific Antibodies of Antipneumococcus Sera, Boston M. & S. J. **190**:819, 1924.

3. Henderson, Yandell, and Haggard, H. W.: The Elimination of Carbon Monoxide from the Blood After a Dangerous Degree of Asphyxiation, and a Therapy for Accelerating the Elimination, J. Pharmacol. & Exper. Therap. **16**: 11, 1920.

Gas Association, Henderson and Haggard [4] stated that in a group of forty-three patients who survived gassing, the records of Bellevue Hospital show that in fourteen subsequent pneumonia developed and ten died. In not a single patient treated by the inhalation of carbon dioxide and oxygen did post-asphyxial pneumonia develop. They observed no harmful accessory features from the inhalation of carbon dioxide.

In 1929, Coryllos and Birnbaum,[5] on the basis of experiments on dogs, considered lobar pneumonia to be a pneumococcic lobar atelectasis. Through bronchoscopic investigations on dogs they observed that infection of the walls of the air tubes produces an excessive and sticky secretion which tends to shut off the portion of the lung to which it leads. As the air in the involved part becomes absorbed, atelectasis develops, secretions accumulate back of the occlusion and consolidation follows.

In 1929, Henderson and Haggard [6] advocated hyperventilation of the lungs as a prophylactic measure against pneumonia. They stated:

> Hyperventilation of the lungs by deep breathing under inhalation of carbon dioxide in proper dilution has proved effective in the prevention of postoperative pneumonia. It is effective also in the prevention of the pneumonia that may follow carbon monoxide asphyxia in untreated cases.

In 1930, Lincoln Brown [7] made bronchoscopic observations on patients with postoperative atelectasis while they inhaled carbon dioxide. He stated:

> Carbon dioxide inhalations when observed through the bronchoscope were seen to: (*a*) increase the rate and depth of respiration; (*b*) produce violent movements in the tracheobronchial tree and alterations in the shape of the lumens of its branches, thereby tending to free adherent mucus; (*c*) induce a distinct blanching of the mucous membranes of the trachea and bronchi.

The first paper on the use of carbon dioxide and oxygen in the treatment of pneumonia was published by Henderson, Haggard, Coryllos, Birnbaum and Radloff,[8] in January, 1930. Their work was

---

4. Henderson, Yandell, and Haggard, H. W.: The Treatment of Carbon Monoxide Asphyxia by Means of Oxygen and Carbon Dioxide Inhalation, Report I, Commission on Resuscitation from Carbon Monoxide Asphyxia to the American Gas Association, J. A. M. A. **79**:1137 (Sept. 30) 1922.

5. Coryllos, P. N., and Birnbaum, G. K.: Lobar Pneumonia Considered as Pneumococcic Lobar Atelectasis of the Lung: Bronchoscopic Investigation, Arch. Surg. **18**:190 (Jan.) 1929.

6. Henderson, Yandell, and Haggard, H. W.: Hyperventilation of the Lungs as a Prophylactic Measure for Pneumonia, J. A. M. A. **92**:434 (Feb. 9) 1929.

7. Brown, A. L.: Bronchoscopic Observations in Postoperative Atelectasis: Action of Carbon Dioxide, J. A. M. A. **95**:100 (July 12) 1930.

8. Henderson, Yandell; Haggard, H. W.; Coryllos, P. N.; Birnbaum, G. L., and Radloff, E. M.: The Treatment of Pneumonia by Inhalation of Carbon Dioxide: I. The Relief of Atelectasis, Arch. Int. Med. **45**:72 (Jan.) 1930.

confined to experiments on dogs. These observers produced experimentally an obstructive atelectasis in dogs and relieved the condition promptly by short periods of inhalation of carbon dioxide and oxygen. They placed their dogs in closed chambers containing approximately 7 per cent carbon dioxide and 93 per cent oxygen. The dogs inhaled this gaseous mixture for periods varying from thirty minutes to one hour. As a result of the experiments, these observers considered pneumonia to be an atelectatic condition and could produce it by insufflation of virulent cultures of pneumococci directly into the bronchi of dogs. They called this condition a pneumococcus atelectasis and considered it to be identical with clinical pneumonias. These dogs were likewise placed in closed chambers containing approximately 7 per cent carbon dioxide and 93 per cent oxygen. They remained for periods of from thirty minutes to twenty-four hours. The pneumonia seemed to clear in some of the dogs.

CLINICAL INVESTIGATIONS

In November, 1930, we began investigations of the treatment of patients with lobar pneumonia with inhalations of carbon dioxide and oxygen.

Administration of Gas.—The real problem was to select apparatus suitable to administer the gas to human patients. A Miller inhaler anesthetic mask and rebreathing bag were selected. The mask is constructed with two sets of valves which can be adjusted so that the patient inhales gas from the rebreathing bag and exhales it into the atmosphere. The gas thus flows in one direction and its concentration in the bag remains constant throughout the inhalation.

The gas was purchased previously mixed and analyzed so that each cylinder contained a mixture of 5 per cent carbon dioxide and 95 per cent oxygen. The problem of dosage then arose; that is, how long to administer the gas and how often to repeat it. We tried to secure this information by observing the effects on four normal persons, who inhaled the gas for periods of ten minutes. Each subject had the same experience of feeling slightly faint at the end of the period but recovered quickly, with no ill after-effects. Kymographic tracings taken during the inhalations revealed that respiration was increased from two to three times in depth and slightly in rate. The determinations of the pulse rate and blood pressure varied but slightly.

With this information, it was decided that patients with pneumonia could probably inhale the gas for a period of ten minutes, and that it could probably be given twice a day. The hours of administration were set arbitrarily at 8 a. m. and 8 p. m. Fourteen patients were treated on this schedule. The dosage was then increased. The remaining thirteen patients received gas for a period of ten minutes at 8 a. m. and 8 p. m., and for two additional periods of five minutes each at 12 noon and 4 p. m.

Selection of Patients.—The criterion for selecting patients was that they should be in an early stage of lobar pneumonia, which could be verified by the history, physical examination or roentgenologic examination. Patients were selected from the medical wards and were rejected if the illness exceeded three days. Otherwise,

no discrimination was made on a basis of probability of recovery. Only patients in the early stages of the disease were chosen, because by daily roentgenologic examination the spread of the pneumonic process in the involved lung could be determined. It is obvious that in late cases with complete consolidation this fact could not be determined.

Routine of Procedure.—Patients admitted with early symptoms of lobar pneumonia were questioned carefully about the duration and nature of their illness. They were then examined to localize the pneumonia. The findings were checked by roentgenologic examination. If evidence of an early pneumonia could be determined, the patient was added to the series for treatment. The inhalations were supplemented by the usual nursing on the wards, an increase of the intake of fluid with dextrose, the use of codeine if needed for restlessness and an attempt to control distention by a daily saline enema. The sputum was typed, and blood cultures were taken. The physiologic effects of the gas on the pulse rate, respiratory rate and blood pressure were recorded before, during and after each inhalation. An occasional estimation of the number of white blood cells was made before, during and after inhalations. Determinations of the vital capacity were made on the last thirteen patients before and after each inhalation. Finally, the sensations of the patient, such as headache, dizziness, fatigue and pleural pain, were recorded with each inhalation of gas.

Except when very ill, the patients were carried to the x-ray room daily for examination.

REPORT OF SERIES

Our series consisted of twenty-seven patients. A summary of the case reports is given in the accompanying table.

There were twenty-two male and five female patients. The age limits varied between 14 and 46 years. The average duration of illness before admission to the hospital was two days.

The site of the pneumonia in the involved lung was as follows: right upper lobe, seven cases; right middle lobe, seven cases; right lower lobe, ten cases; left upper lobe, six cases; left lower lobe, ten cases. There was one case of pneumonia of the right hilus. The pneumonia spread to one or more lobes in nine patients of the series.

The gas was given on an average of five and one-half days. The shortest period of administration was three and one-half days, the longest ten and one-half days.

The disease ended by crisis in twenty-four patients, and by lysis in three.

Sputum was typed in each case, with the following results: type I, one case; type II, two cases; type III, four cases; type IV, eleven cases; mixed, two cases; undetermined, seven cases.

There were fifteen positive blood cultures. The pneumococcus was recovered in seven cases, the streptococcus in two cases, the staphylococcus in three cases and the diphtheroid bacillus in three cases.

Determinations of the vital capacity served as a valuable guide as to the degree of consolidation and as an index of spread to other lobes.

Summary of Case Reports

Patient	Age	Sex	Days Ill	Lobes Involved	Spread to Other Lobes	Days Gas Given	Day of Crisis	Type From Sputum	Blood Cultures	Sensations	Complications	Deaths
1	46	F	2	Right lower	None	6	6	...	Pneumococcus	Took gas well	Diabetes mellitus	..
2	38	M	1	Left upper	None	5	3	...	Negative	Headache; pain in chest	None	..
3	23	F	3	Left lower	Left upper	6	Lysis	...	Streptococcus	Took gas well	Empyema	..
4	16	M	2	Right middle	None	4	2	...	Undetermined	Headache; pain in chest	None	..
5	18	M	2	Right upper	None	5	Lysis	IV	Negative	Took gas well	None	..
6	16	M	1	Left lower	None	8	7	...	Diphtheroid	Took gas well	None	..
7	26	M	2	Right middle	None	5	4	...	Negative	Pain in chest	None	..
8	35	M	2	Left upper and lower	None	7	5	Mixed	Pneumococcus	Fatigue	None	..
9	45	M	2	Left lower	None	3½	3	IV	Negative	Slight fatigue	None	..
10	29	M	1	Right lower	None	3½	2	III	Undetermined	Took gas well	None	..
11	35	F	3	Left lower	Left upper	6	..	IV	Streptococcus	Headache	Puerperal sepsis; miscarriage	+
12	19	M	2	Left lower	Left upper; right upper	6½	6	IV	Pneumococcus	Headache; fatigue	Empyema	..
13	15	M	2	Left lower	Right upper; right middle; right lower	10½	7 14	II	Staphylococcus	Took gas well	None	..
14	30	M	1½	Right upper	None	5	6	IV	Pneumococcus	Headache	Hypertension	..
15	17	M	1	Right lower	Right middle	7½	7	...	Staphylococcus	Took gas well	None	..
16	25	M	1	Right lower	None	6	8	III	Pneumococcus	Took gas well	None	..
17	33	M	3	Right upper	Right middle	8	11	III	Pneumococcus	Slight headache	None	..
18	25	M	3	Right lower	None	6½	4	I	Pneumococcus	Took gas well	None	..
19	20	M	3	Left upper and lower	None	4	2	IV	Negative	Took gas well	None	..
20	30	F	1	Right hilus	None	5	4	III	Diphtheroid	Took gas well	Pansinusitis	..
21	16	F	2	Right middle	Right lower	6	2	Mixed	Negative	Took gas well	None	..
22	18	M	3	Right upper	None	7	7	IV	Negative	Took gas well	None	..
23	21	M	2	Right upper	Right middle and lower	6	5	IV	Negative	Took gas well	None	..
24	14	M	2	Right lower	None	4	3	II	Negative	Headache	None	..
25	19	M	2	Right lower	None	6	6	IV	Diphtheroid	Headache; pain in chest	Pericarditis	+
26	30	M	1	Left lower	None	4	..	IV	Undetermined	Took gas well; cough	Empyema	..
27	30	M	3	Left lower	Left upper	7½	Lysis	IV	Staphylococcus			

There was no constant response of the white blood cells before, during or after inhalations. The number was increased at times, while at other times it was decreased during inhalations.

The most common sensation experienced while the patients were inhaling the gas was headache. Seven patients complained of moderate to severe headache. Pleural pain was experienced by nearly all of the patients at the beginning of each inhalation but was not severe enough to be a contraindication for its use. Four patients complained of severe pleural pain. The majority of patients experienced some fatigue during inhalations, and when this was severe the periods of administration were shortened, much to the comfort of the patient. One patient had severe cough as a result of inhaling the gas. Administration was stopped because in this patient subsequent empyema developed. Sixteen patients took the gas well and experienced considerable relief from symptoms through its use.

COMMENT

The results of our series are interesting, though not dramatic. The series is small. We were unable to run a control series of early cases, owing to an inability to get patients in the early stages of the disease. From Nov. 15, 1930, to April 21, 1931, 114 patients ill with lobar pneumonia were admitted to the medical wards. Of these, twenty-seven were selected as suitable for treatment with carbon dioxide and oxygen. In this group there were two deaths, constituting a mortality of 7.4 per cent. The remaining eighty-seven patients were in various stages of pneumonia. Some of the patients were in the early stage of the disease, while others were in the advanced stage. The latter group was heterogenic so far as treatment was concerned. There were six patients who died within twenty-four hours and nineteen patients who received vaccine therapy without our supervision. Deducting these twenty-five, there remain sixty-two patients who received supportive treatment only. In this group there were twenty-two deaths. The mortality rate for this group was 35.9 per cent. A comparison of the death rates in the two groups is not justified as the effects of carbon dioxide and oxygen were not tried on patients in the moderately advanced or advanced stages of the disease.

Our investigations indicate that with the dosage and apparatus used, early pneumonia could not be aborted. The earliest evidence of pneumonia in some x-ray pictures was an interlobar pleurisy. Even with inhalations, from partial to complete consolidation occurred. Other films showed a mottling that proceeded to various stages of consolidation. There was no marked difference in the films of either half of the series, although in the last thirteen cases in which the gas was administered four times daily, there was apparently less tendency for

consolidation to occur. In several of these patients the pneumonia seemed to be held essentially in its original stage.

The tendency to spread to other lobes occurred about equally in both groups of the series. There were four instances of spread in the first half of the series and five instances of spread in the latter half.

Empyema occurred twice in patients receiving two inhalations daily and once in patients receiving four inhalations daily.

There was one death in each group. The first death occurred in case 2, in which pneumonia was complicated by puerperal sepsis and streptococcus septicemia. The second death occurred in case 26, in which pneumonia was complicated by a terminal pericarditis.

In the series as a whole, there were no appreciable effects on the pulse rate and blood pressure taken before, during and after each inhalation. Slight increases or decreases occurred in each at times, but they were of minor variation. Respiration was usually doubled or trebled in depth and increased slightly in rate.

Hypertension was not a contraindication for the use of the gas, as was seen in case 14, in which the blood pressure was 165 systolic and 120 diastolic. Carbon dioxide and oxygen caused only minor variations in this patient's blood pressure, and he made an uneventful recovery.

The effect on cyanosis was difficult to determine as all the patients were Negroes.

The patients invariably stated that they could breathe deeper and more easily immediately after each inhalation. Pleural pain was no contraindication. The pain was usually increased at the beginning of each inhalation, but subsided, as a rule, during administration of the gas. In some patients, the pain was relieved for from one to three hours after administration. In others, the gas had a sedative effect and the patients wanted to sleep. In none of the patients were chest swathes used, the thorax being left free to expand fully with each inspiration.

SUMMARY

1. Twenty-seven patients suffering with early lobar pneumonia were treated with inhalations of 5 per cent carbon dioxide and 95 per cent oxygen. There were two deaths.

2. So far as we could determine, inhalation of carbon dioxide and oxygen in this concentration is accompanied by no harmful effects.

3. The dosage and method of administration should be investigated further before inhalation of these gases is advocated for practical use in the treatment of pneumonia.

478 Peachtree Street, N. E.

QUININE DERIVATIVES AND SPECIFIC IMMUNE SERUM IN THE TREATMENT OF PNEUMOCOCCUS INFECTION

HOBART A. REIMANN, M.D.
AND
JOHANNES K. MOEN, M.D.
MINNEAPOLIS

From the replies returned by twenty-five prominent German clinicians in response to questionnaires,[1] it is evident that specific treatment of lobar pneumonia with immune serum has not as yet been generally accepted. Even in this country, an inquiry revealed that many physicians still rely on quinine derivatives and do not employ specific immune serum in treating lobar pneumonia. In view of the reports of Cole,[2] Cecil and Sutliff,[3] Park, Bullowa and Rosenbluth [4] and others, showing the beneficial effects of type I serum in treating type I infections in a large number of patients, it seems unfortunate that quinine is still being used to the exclusion of specific serotherapy.

Quinine was introduced in the treatment of pneumonia about fifty years ago, chiefly by Jürgenson and Aufrecht. A new compound, ethylhydrocupreine, was popularized by Morgenroth and his associates in 1911. Ethylhydrocupreine is more pneumococcicidal than quinine in vitro even in the presence of serum, which ordinarily protects pneumococci against bactericides. The studies of Moore [5] and of Baldwin and Rhoades [6] corroborate the reports of the effectiveness of ethylhydrocupreine in vitro, and their statements are used by commercial interests to promote the use of the drug in pneumonia. Clinical reports concerning the beneficial effects of optochin or quinine in the treatment of pneumo-

From the Department of Medicine, University of Minnesota.

1. Med. Klin. **25**:1771 and 1811, 1929; Deutsche med. Wchnschr. **56**:566, 1930.

2. Cole, Rufus: Serum Treatment in Type I Lobar Pneumonia, J. A. M. A. **93**:741 (Sept. 7) 1929.

3. Cecil, R. L., and Sutliff, W. D.: The Treatment of Lobar Pneumonia with Concentrated Antipneumococcus Serum, J. A. M. A. **91**:2035 (Dec. 29) 1928.

4. Park, W. H.; Bullowa, J. G. M., and Rosenbluth, M. B.: The Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum, J. A. M. A. **91**:1503 (Nov. 17) 1928.

5. Moore, H. F.: J. Exper. Med. **22**:551, 1915.

6. Baldwin, H. S., and Rhoades, D. R.: Hygienic Laboratory Bulletin, 1925, p. 69.

nia are, for the most part, unconvincing. Baldwin [7] has since devoted his attention to specific serotherapy of the disease. Cross,[8] in a recent publication favoring the use of ethylhydrocupreine, stated that his impressions in regard to the efficacy of the drug were based chiefly on clinical and bedside impressions. Such criteria are, as a rule, too unreliable for use as scientific data. Convincing evidence can be obtained only from careful studies showing a shortening of the duration of the disease, a diminution or elimination of bacteremia and a reduction of the mortality, such as have been demonstrated in the use of specific serum. Furthermore, it is impossible to evaluate the results of most studies of patients treated with quinine derivatives since in practically none have attempts been made to classify pneumonia on an etiologic basis in regard to type of pneumococcus.

If one considers the replies of the German physicians who have used serotherapy and found it valueless, it is evident that none of them have given univalent serum in large doses, intravenously, according to the method prescribed by Avery, Chickering, Cole and Dochez.[9] Most of them used polyvalent immune serum and administered small doses intramuscularly. Only a few mentioned that efforts had been made to ascertain the type of pneumococcus beforehand. Professor Krehl, practically the only one to recommend serum therapy, determined the type of pneumococcus in his cases and administered immune serum intravenously with encouraging results. Fourteen of the twenty-five physicians questioned, including Sahli, von Bergmann, Eppinger, Curschmann and Schittenhelm, stated that they used quinine or its derivatives solvochin, transpulmin, plasmochin and ethylhydrocupreine exclusively. Of these drugs, solvochin [10] and transpulmin [11] have been found unacceptable for inclusion in "New and Nonofficial Remedies" by the Council on Pharmacy and Chemistry of the American Medical Association. Several of the clinicians saw no reason to introduce serum therapy in the face of the satisfactory results obtained from quinine. Of the remaining eleven, some did not have enough experience with serotherapy to give an opinion as to its worth, one (F. Meyer) stated that he uses serum and optochin in combination, and one (Weinberg) was skeptical of both serum and quinine therapy.

7. Baldwin, H. S.: M. Clin. North America **12**:679, 1928.

8. Cross, F. B.: M. J. & Rec. **116**:271 and 354, 1927.

9. Avery, O. T.; Chickering, H. T.; Cole, R. I., and Dochez, A. R.: Monograph no. 7, Rockefeller Institute for Medical Research, 1917.

10. Council on Pharmacy and Chemistry: Solvochin Not Acceptable for N. N. R., J. A. M. A. **96**:1477 (May 2) 1931.

11. Council on Pharmacy and Chemistry: Quicamphol (Transpulmin) Not Acceptable for N. N. R., J. A. M. A. **93**:1471 (Nov. 9) 1929.

Because of the preponderance of opinion in favor of quinine in the treatment of pneumonia expressed by these German clinicians, and since quinine preparations are widely advertised as specific for lobar pneumonia, it was considered timely to retest the effects of quinine on controlled pneumococcus infection and to compare its effects with those of specific immune serum. For this purpose, the new satisfactory method of inducing pneumococcus infection developed by Goodner [12] was employed. This method affords, under experimental conditions, a symptom complex that is analogous in several respects to lobar pneumonia in man. The method also renders it possible to observe and to compare the effects of various methods of treatment.

"Dermal" pneumonia is produced in rabbits by injecting small amounts of pneumococcus culture intradermally. A local lesion of the skin develops after eight to twelve hours which, histologically, resembles the reaction found in the human pneumonic lung. In from twelve to twenty-four hours, shortly after the appearance of the skin lesion, bacteremia and high fever develop (see chart 1 *B*). In untreated animals that die, the organisms in the blood increase in number; in animals that recover, the blood stream may never be invaded, or if pneumococci are present, they disappear. In Goodner's series of fifty-six untreated rabbits, forty-eight died, a mortality of about 80 per cent. If, however, specific antipneumococcus serum is given early in the course of the disease in sufficiently large doses, the organisms disappear from the blood, the temperature drops, and the animal usually recovers.

EXPERIMENTAL METHODS

Strains of type I and type II pneumococci obtained from the Hospital of the Rockefeller Institute, through the kindness of Dr. Avery, were used. Healthy rabbits were inoculated intradermally in the shaved skin of the abdomen with 0.2 cc. of a 1:1,000 dilution of an eighteen hour broth culture of pneumococci. Rectal temperatures were recorded at least twice daily thereafter, and blood cultures were made once or twice daily until the animal recovered or died. Blood cultures were made by obtaining, accurately, from 0.1 to 0.2 cc. of blood from the marginal vein of the ear, mixing it with 15 cc. of nutrient agar containing 0.5 cc. of sterile blood, at 45 C., and pouring plates. In this manner, the number of colonies of pneumococci could be counted after twenty-four hours' incubation, permitting a quantitative estimation of the intensity of the bacteremia.

Two quinine preparations were tested, quinine hydrochloride and ethylhydrocupreine (optochin base, "New and Nonofficial Remedies"), since these are the substances most commonly used clinically. Quinine hydrochloride was dissolved in distilled water and administered intramuscularly and intravenously. The dose given intramuscularly approximated the tolerated dose of from 30 to 70 mg. per kilogram, as given by Solis-Cohen, Kolmer and Heist.[13] As a rule, 50 mg. per kilogram

12. Goodner, K.: J. Exper. Med. **48**:413, 1928.

13. Solis-Cohen, S.; Kolmer, J. A., and Heist, G. D.: J. Infect. Dis. **20**:313, 1917.

of body weight was given within eight hours in divided doses. In one instance, a rabbit died shortly after the injection of 50 mg. per kilogram, but in some animals, as much as 120 mg. per kilogram was given in three doses of 40 mg. each at four hour intervals without evidence of poisoning. Quinine hydrochloride was given intravenously in divided doses so as to inject 30 mg. per kilogram within eight hours. The tolerated dose is stated to be from 20 to 30 mg., and the lethal dose 50 mg., per kilogram.[13]

The water-insoluble ethylhydrocupreine was dissolved in olive oil. Two per cent solutions were used. The solution was injected subcutaneously so that 150 mg. per kilogram was given in divided doses. One animal received 275 mg. per kilogram in forty-eight hours. Ethylhydrocupreine in 2 per cent solution in olive oil was also injected directly into the stomach by means of a ureteral catheter. Rabbits received 400 mg. of ethylhydrocupreine in two doses within four hours. To three animals, 200 mg. was again given the following day, making a total of 600 mg. This amount is approximately one fourth of the total dose (2.4 Gm.) recommended for human beings for a similar period of time (Cross[8]). The insolubility of ethylhydrocupreine in water and its low solubility in oil precluded intravenous or intramuscular therapy. Blood cultures were made before and after the commencement of treatment, in most cases twice daily.

A potent antipneumococcus (horse) serum was administered intravenously within the first few hours after the onset of fever. The dose recommended by Goodner was used—0.23 per cent of the body weight. In some cases, the dose was repeated once or twice the same day. Blood cultures and registrations of temperature were made as in the observations with drugs.

In most experiments, sets of four rabbits were studied; two animals were treated, and two served as controls.

RESULTS

The strain of type I pneumococci used in these experiments proved to be exceptionally virulent for rabbits. All of the seventeen untreated control rabbits died. Death usually occurred on the first or second day after inoculation. Bacteremia was present in each case. The strain of type II pneumococci was less virulent; eight of eleven inoculated rabbits survived. Bacteremia did not occur in any.

Effect of Quinine Therapy.—Although large doses of quinine hydrochloride and of ethylhydrocupreine were given early in the course of infection, all of the twenty-two rabbits thus treated succumbed to infection. Nine died one day after inoculation, eleven two days after and two three days after, which was similar to the behavior of the untreated controls. A typical experiment is illustrated in chart 1 *A*.

Although large doses of ethylhydrocupreine were given, bacteremia persisted unaffected, and the animal died in two days. In none of the experiments, except one, was there any evidence of diminution of fever or of prolongation of life as compared with the controls. In all animals infected with type I pneumococci bacteremia developed, and in none, except one, treated with quinine salts was there any evidence of effect on the bacteremia. In the one exception, the temperature dropped to normal,

and the bacteremia diminished from 1,000 to 10 colonies per cubic centimeter of blood following an intramuscular injection of 120 mg. of quinine hydrochloride, which is double the usual tolerated dose. The bacteremia and fever both increased rapidly again, within a few hours, and the animal died on the third day. In many instances, the number of circulating organisms increased during the treatment until death occurred.

We were unable to demonstrate any appreciable effect of quinine salts on the course of pneumococcus infection in rabbits. No difference was noted in relation to the route of injection of the drugs, nor were any differences noted between the effects of quinine hydrochloride and those of ethylhydrocupreine. All of the twenty-two treated and seventeen untreated rabbits died.

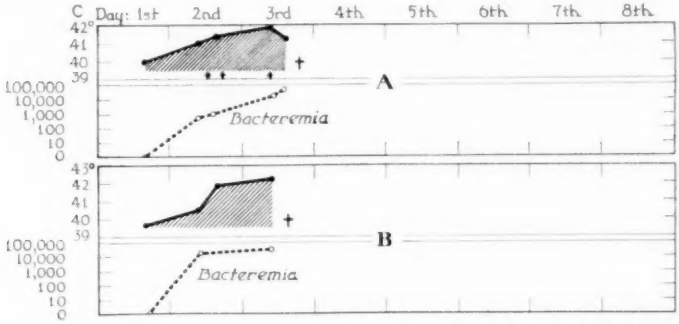


Chart 1.—The temperature curve and the number of pneumococci per cubic centimeter of blood at various intervals in a rabbit (*A*) treated with ethylhydrocupreine, as indicated by the arrows, and in an untreated control rabbit (*B*).

In animals inoculated with type II pneumococci, ethylhydrocupreine was likewise without effect. A typical experiment is illustrated in chart 2 *C*. As shown in the chart, one rabbit (*C*) received two doses of 200 mg. of ethylhydrocupreine base per kilogram, but died five days after inoculation. The control animal (*D*) recovered on the sixth day. In another experiment, four rabbits all recovered from infection on the fourth or the fifth day. The course of the infection in the two animals treated with quinine was no different from that in the two controls.

Effect of Serotherapy.—Since the striking therapeutic effects of specific immune serum duplicated the results reported by Goodner, only a few animals were thus treated. Several experiments were performed, with sets of four rabbits each. In two experiments there were two treated and two control animals. All of the controls died. Of the four treated animals, two recovered. In one of the two treated animals that died, the temperature dropped to normal and the pneumococci in the

blood stream diminished in number from 50,000 to 1,000 per cubic centimeter after one injection of serum. The next day, however, fever again appeared, bacteremia increased, and the rabbit died. A second dose of serum on the second day failed to save the animal. It is possible that repetition of the treatment within a few hours after the first dose would have saved both animals. In another experiment, all four rabbits were treated with serum. In each, bacteremia greatly diminished or disappeared after the first injection. In two, about 10 colonies per cubic centimeter reappeared when the next blood culture was made, but disappeared after the second and third injections of serum. One rabbit

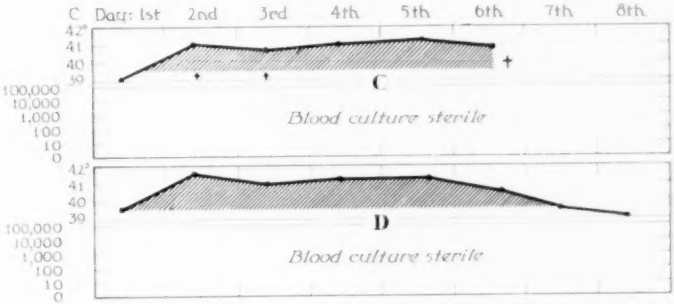


Chart 2.—The absence of effect of ethylhydrocupreine in a rabbit (*C*) infected with type II pneumococci and treated with ethylhydrocupreine, as indicated by the arrows, compared with a similarly infected but untreated control rabbit (*D*).

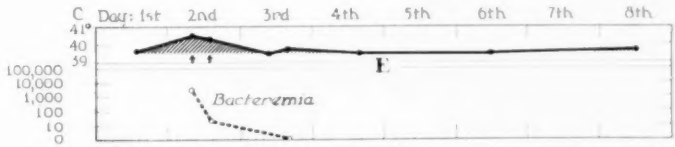


Chart 3.—The therapeutic effect of type I serum administered to a rabbit (*E*) infected with type I pneumococci. The rabbit (1,800 Gm.) received two intravenous injections of 4 cc. each, as indicated by the arrows.

recovered on the first day and one on the second day; in one, fever persisted for four days before recovery. The fourth rabbit apparently recovered, the temperature dropped to normal on the second day, and the blood culture became sterile, but on the third day it was found dead. Necropsy revealed pneumococcic pericarditis.

The striking beneficial effects of specific immune serum in most of the treated rabbits was demonstrated by the reduction of fever and the elimination of bacteremia. Of eight animals treated with immune serum, five recovered. The record of one of the rabbits successfully treated with specific immune serum is illustrated in chart 3 *E*.

COMMENT

The results of the experiments leave no doubt as to the superiority of specific immune serum in the treatment of pneumococcus infection in rabbits. Quinine hydrochloride and ethylhydrocupreine, although pneumococcicidal in vitro, appear to have no effect on the course of the infection, on the bacteremia or on the outcome as compared with the controls. All of the twenty-two rabbits treated with quinine derivatives and all of the seventeen untreated animals died in approximately the same length of time after inoculation with type I pneumococci. On the other hand, five of eight animals treated with specific immune serum recovered.

Quinine salts had no influence on the course of the milder infections due to type II pneumococci. Treated and control animals recovered in approximately the same length of time.

CONCLUSIONS

Quinine hydrochloride administered intravenously or intramuscularly and ethylhydrocupreine administered subcutaneously and by mouth had no effect on the course of experimental pneumococcus infection in rabbits.

Specific immune serum, when given intravenously early in the course of infection in adequate doses, eliminates pneumococci from the blood stream, reduces the fever and causes recovery in most of the treated animals.

RESUSCITATION OF THE STOPPED HEART BY INTRACARDIAL THERAPY

II. EXPERIMENTAL USE OF AN ARTIFICIAL PACEMAKER

ALBERT S. HYMAN, M.D.
Director, Witkin Foundation for the Study and Prevention of Heart Disease, Beth David Hospital
NEW YORK

Cardiac standstill, regardless of the sequential development of the etiologic factors responsible for its occurrence, constitutes a clinical problem of no little magnitude so far as a favorable outcome in any individual case is predicated on the initiation of therapeutic measures leading to prompt restoration of the automatic activity of the heart. The more or less dramatic events attending cardiac arrest, whether the scene be laid in a well appointed hospital operating amphitheater, a doctor's consulting room or in less favorable circumstances, are always associated with ill defined attempts to do something to restore cardiac function. In the brief interval before complete surrender to death has taken place and before utter helplessness has seized those administering to the dying person, many random and badly executed procedures are invoked with the last minute hope of resuscitating the stopped heart.

In a previous communication [1] I attempted to review the methods currently employed in restoring normal cardiac activity. It was pointed out that when complete asystole of the heart occurs, a relative anoxemia of the myocardium soon develops; as this disturbed chemical balance progresses, the irritability factors of the heart muscle as a whole are markedly altered, so that the physiologic response to stimuli initiated outside of the normal pacemaker area at the sino-auricular node is enhanced. Any external mechanical stimulus when applied directly to the heart may result in an ectopic contraction; there is considerable experimental evidence to indicate that the first beat under such circumstances is always extrasystolic (fig. 6).

In the early phase of the anoxemic period, the development of a single ectopic contraction may be, and usually is, sufficient to restore normal sinus rhythm. Medical literature is replete with instances of

Published by permission of Grant No. 21A from the Witkin Foundation.
Report of the Special Committee on Intracardiac Therapy of the Witkin Foundation.

1. Hyman, Albert S.: Resuscitation of the Stopped Heart by Intracardiac Therapy, Arch. Int. Med. **46**:553 (Oct.) 1930.

resuscitation by such mechanical stimulation of the stopped heart. Surgeons have massaged the heart when it has stopped beating during the course of an operation; squeezing, pinching or any other manipulation that directly develops a focal point of irritability from which an extrasystolic beat can arise permits the heart to return to its own automatic activity.

The past decade has seen another and a perhaps more direct measure introduced into clinical medicine. Intracardial injection therapy has, since 1921, received more and more attention as a procedure in resuscitating the stopped heart. Many instances of recovery after the intracardial injection of epinephrine have been recorded in the literature; up to 1930, my previous report showed that there were about 250 cases in which intracardial therapy in one form or another had been resorted to, with a favorable outcome in about 25 per cent. Many other substances in addition to epinephrine—twelve have been described—when injected during the early anoxemic phase of the asystolic heart will cause extrasystolic contractions and in suitable cases a complete return to normal auriculoventricular rhythm.

The indications for such intracardial injection therapy are rather clearly defined. Meyer's [2] classification of cardiac arrest divided all such instances into two groups: First are those in which the patient has died as the result of constitutional or infectious disease processes. For these, no favorable outlook is to be anticipated as the heart is no longer normal, having been concomitantly altered by severe pathologic changes in other parts of the body. The second group of patients, comprising those who have died on the operating room table, the street or the battle field as the result of shock, pacemaker disturbance or an unstable vagal mechanism, may be resuscitated by intracardial therapy as these hearts are fundamentally normal and unaffected by such pathologic changes as those in the former group. In other words, intracardial injection should be a mode of therapy available for persons free from cardiovascular disease who have suffered sudden "death" from one of the aforementioned causes.

The success of such intracardial injection procedures, regardless of the substance used, although epinephrine is by far the most popular, is due entirely to the prick of the needle thrust into the heart. Here again, a focal point of irritability is generated in the heart muscle from which ectopic beats may be initiated. As already indicated, in the first phase of the anoxemic period the extrasystole, regardless of its site of origin, is usually promptly followed by sinus rhythm. When, however, the anoxemic period extends into its second phase and when the chemical changes in the various structures of the heart have become so altered

2. Meyer, C.: Jahrb. f. Kinderh. **107**:76 (Sept.) 1924.

that the electrodynamic factors are irreversibly disturbed, such a point of focal irritability may persist and continue to initiate stimuli for many other extrasystoles. Instead of one ectopic beat there will be a long series of rapidly developing extrasystoles which may approach paroxysmal tachycardia. When the ectopic focus has developed in the ventricles as the result of the intracardial injection therapy, paroxysmal ventricular tachycardia can be quickly followed by ventricular fibrillation and then by vascular collapse and death.

It was for this reason that we suggested that the intracardial injection be made into the right auricle; here the same phenomena may take place. Extrasystoles rapidly initiated may pass quickly into paroxysmal auricular tachycardia and then into auricular fibrillation. The difference in this instance is that while ventricular fibrillation is incompatible with life, auricular fibrillation is a well known and easily handled clinical entity. The rationale of intra-auricular puncture is thus based on physiologic principles and may offer a favorable outcome in cases in which cardiac arrest has occurred in an otherwise normally functioning system.

Since the publication of the original paper in 1930, there has apparently been a rather general acceptance of our conception of the procedure of intracardial injection. Reviews and comments both here[3] and abroad,[4] as well as the more recent textbooks on the heart (for example, those of East and Bain[5] and Paul D. White[6]), have all served to focus attention on the desirability of utilizing this type of resuscitation therapy when indicated. The preferential site of the injection has also been discussed by several authors; the unqualified adoption of intra-auricular puncture has been recommended by some,[7] while it has been held inadvisable by others.[8]

Opportunity for further investigation of the problem has been generously afforded through an additional grant from the Witkin Foundation; experimental studies on certain physiologic functions of the disturbed heart muscle during the various phases of anoxemia

3. These reviews and comments were published in the following journals: J. A. M. A. **95**:1939 (Dec. 20) 1930. Am. Heart J. **6**:302 (Dec.) 1930. Canad. M. A. J. **24**:462 (March) 1931. Practical Medicine Series: General Medicine, p. 593; General Surgery, p. 24; General Therapeutics, p. 48, Chicago, Year Book Publishers, 1931.

4. A review appeared in Lancet (**2**:83 [Jan. 10] 1931) and also in the Zentralblatt für innere Medizin (**60**:544 [March 23] 1931).

5. East, C. F., and Bain, C. W.: Recent Advances in Cardiology, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1931, p. 254.

6. White, Paul D.: Heart Disease, New York, The Macmillan Company, 1931, p. 875.

7. Intra-Auricular Puncture, editorial, J. A. M. A. **96**:1875 (May 30) 1931.

8. Henderson, Y.: Intracardiac Therapy, correspondence, J. A. M. A. **97**:124 (July 11) 1931.

resulting from cardiac arrest have been attempted, and several general conclusions have become permissible. The first of these is that the anoxemia which immediately takes place in the heart muscle with the onset of ventricular standstill reaches a relatively high acid concentration within a brief interval; many laboratory investigators have shown that the curve of p_H concentration rises rapidly in heart muscle when the normal circulatory mechanism is disturbed.

Further studies have demonstrated that as the curve of p_H concentration rises, the rate of electric conductivity is markedly enhanced; in the beginning the two curves run almost parallel, but after a certain well defined interval the curve of conductivity rises much slower than the curve of acid concentration. Regarded from another angle, it may be said that the threshold of conductivity is considerably lowered during the initial stages of myocardial anoxemia. The irritability factors of the heart are thus at first increased, but as the myocardium suffers prolonged oxygen-want and increasing acid overbalance, there is a breakdown of the normal electrodynamic factors, so that there is no coordinated fiber response and muscle contraction.

During the period of hyperirritability mechanical stimulation of any type sufficiently intense enough to reach the heart muscle fibers will be followed by contraction; this contraction will necessarily be of the extrasystolic type since the stimulus for the beat arises outside of the normal pacemaker. We have previously pointed out that the auricles are physiologically better prepared to receive such ectopic stimulation than the ventricles, and that the circulatory demands of the body may be maintained over long periods of time by extrasinus nodal rhythms.

While it is true that ordinarily a single prick of the needle may be enough to produce a point from which stimuli for myocardial contraction can arise, the success of this procedure depends on the stage of anoxemia through which the entire heart is passing at the time that the injection is attempted. During the initial stages of the resuscitation period the response to such stimulation is almost always positive, but as the middle and later stages of this period are approached and as the electrodynamic balance of the entire heart becomes more and more disturbed, a single prick of the needle may not be sufficiently powerful enough to dominate the complicated physiologic mechanisms that arise. Two or even three or more needle thrusts may be required; the disadvantages of this procedure are obvious. Henderson [8] has already commented on the injury to the heart likely to follow such multiple punctures.

Since the entire phenomenon of stimulus production as the result of the mechanical irritation of the needle prick is dependent on the development of differences in electric potential, it would seem that a

control of the latter factor might favorably affect the chances of myocardial contraction. Moreover, the needle prick under such conditions offers only a single stimulus for the contraction of the heart; in laboratory animals this feature can be readily demonstrated. In a guinea-pig heart, for example, after cardiac arrest occurs and after the resuscitation period enters into its second phase, the needle prick initiates only a single cardiac contraction.

If the electric difference of potential could be rhythmically developed during this period of cardiac standstill, it would appear *a priori* that regular contractions of the heart would follow, and under such artificial stimulus production an automatic activity of the entire heart might be maintained. When such a stimulus center is produced in the auricles, the factor leading to a normal cardiovascular response is to be anticipated, and with the return of a favorable peripheral circulation all the vital organs, unless irreparably damaged, would again take up their normal functions. With the restoration of coronary circulation and with the disappearance of the chemical imbalance the myocardium will again resume its normal activity with the taking up of its own automatic sinus nodal rhythm.

The problems engendered by electrical stimulation of the stopped heart are not new; as long ago as 1862, Walsh[9] discussed the possibilities of causing the heart to contract by faradic stimulation of the sympathetic nervous trunks. Since that time there have appeared no less than sixty-five papers in the medical literature of continental Europe and America, all concerned with various methods of reactivating the heart by electrical devices. For most part, the workers in this field have been interested in the stimulation of the neuromuscular mechanism of the heart, and in the papers written before 1910 the general opinion seems to have been that the heart was subservient to neurologic-electric control.

More recently several authors have attempted to reanimate the asystolic heart by passing electric currents of different types through the chest; both high and low frequency differences of potential have been used and many kinds of electrodes have been employed. Kingsley, for example, has experimented with a diathermic current in which the focal electrode was oriented in the heart muscle; a Japanese worker, in a further development of this theory, believed that increasing the temperature of the heart tissues would enhance the possibility of the restoration of automatic cardiac activity, and in some rather brilliantly performed experiments showed this to be true in laboratory animals.

9. Walshe, W. H.: A Practical Treatise on the Diseases of the Heart and Great Vessels, Philadelphia, Blanchard & Lea, 1862, p. 155.

In 1929, at the Medical Congress held in Sydney, Australia, Gould demonstrated an electric device for stimulating the heart; this apparatus consisted of a neutral plate and a positive needle electrode which was inserted into the heart. Gould reported the case of a baby who was resuscitated by such electrical stimulations of this organ.

Prior to this, in 1927, we developed an apparatus for rhythmically stimulating a heart-lung preparation during a study that was being made on experimentally produced extrasystolic arrhythmias.[10] This apparatus, based originally on the Fiertz-Kaufmann induction coil stimulator familiar in one form or another in all physiologic laboratories, was constructed with a rotary polyphasic interrupter which permitted a known faradic current to be applied directly to the heart muscle. In the course of the experimental work on this subject a special needle electrode was developed, as the ordinary procedures utilize the single point method of stimulation with a neutral electrode grounding the entire heart (Rothberger).

While the studies on intracardiac therapy were being carried out, it occurred to us in April, 1928, that resuscitation of the stopped heart might be secured by applying procedures previously employed only in laboratory animals; at this time the needle prick theory of reactivating the asystolic heart was just being investigated. The replacement of the clinically employed hollow injecting needle by a special needle electrode that would carry a suitable stimulating current to the heart muscle now became a matter for special investigation. Since such a procedure would be, in effect, the employment of an artificial pacemaker acting in many respects like that of the normal sinus nodal pacemaker, there immediately arose the problem of the type and strength of the electric stimulus to be used.

The electrophysical phases of the problem were found to be beyond the scope of our own laboratories, so that assistance was required from several workers in the electrophysical departments of New York University. With their help a suitable apparatus was devised, a description of which follows.

THE ARTIFICIAL PACEMAKER; ITS DESCRIPTION AND MODE OF OPERATION

In its final form the artificial pacemaker scarcely resembles the original cumbersome, complicated and unwieldly apparatus that was developed to carry out the theoretical demands imposed on it for restoration of function of the asystolic heart. These demands can be briefly enumerated as follows: (1) imitation of the normal sinus nodal impulse in difference of electric potential, speed of release, rate of

10. Hyman, A. S.: The Experimental Production of Extrasystoles in the Human Heart, to be published.

discharge and regularity of rhythm; (2) discharge of this current in that part of the heart in which a nearly normal cardiac response would follow; (3) maintenance of rhythmic discharge over a controllable period of time; (4) freedom from the need of accessory and perishable materials, and (5) instant availability for emergency conditions.

Studies involving resistance phenomena in various types of tissue, refractory periods, contractility curves and other stimulant physiologic functions of muscles were made, and certain constants were finally experimentally established. The source of the electric current proved to be one of the greatest problems; realizing that the apparatus was to be used for emergency purposes, it soon became evident that it must

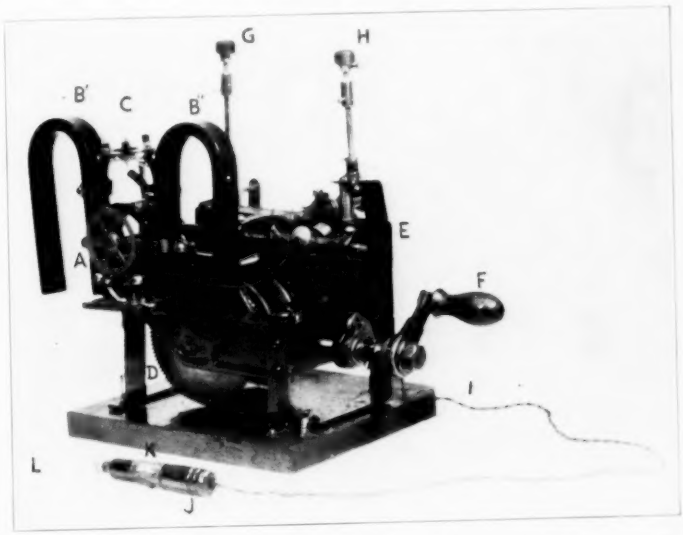


Fig. 1.—The artificial pacemaker seen from the front. In figures 1 to 4 the following important features are to be noted: *A*, magnetogenerator; *B'* and *B''*, companion magnet pieces; *C*, neon lamps; *D*, spring motor; *E*, ballistic governor; *F*, handle; *G*, impulse control; *H*, speed control; *I*, flexible electric cord; *J*, insulated handle; *K*, handle switch, and *L*, electrode needle.

be prepared at all times for instantaneous action. For this reason, the use of batteries of any type was prohibited; the life period of commercial electric batteries, even when they are unused, is only about six months, so that unless new batteries were constantly being inserted, the machine might prove valueless when needed the most. Small generators were devised, only to be rejected because the type of current developed by them was not suitable for this work; moreover, the motive power required to spin these generators was too great to permit their use in a small portable apparatus.

Finally, a special form of magnetogenerator was constructed, with armature windings of sufficient size and number to develop the required stimulating current; an unusual type of built-up magnetic flux and the inclusion of a Tesla controlled break circuit on the armature brought into final fruition a very small and easily turned apparatus. A spring motor connected with appropriate gears and regulated by a ballistic governor was found to spin the generator for a period of six minutes with a remarkable constancy; a ratchet handle made possible rewinding of the motor without appreciably affecting either the speed or the power of the generator. In one experiment, the generator was kept in motion for four hours with no fluctuation in its output.

A rotary two-faced interrupter disk, geared at a definitely determined ratio to the generator armature, controlled the duration and speed of the electric current delivered to the outlet terminals. Three interrupter ratios were arbitrarily

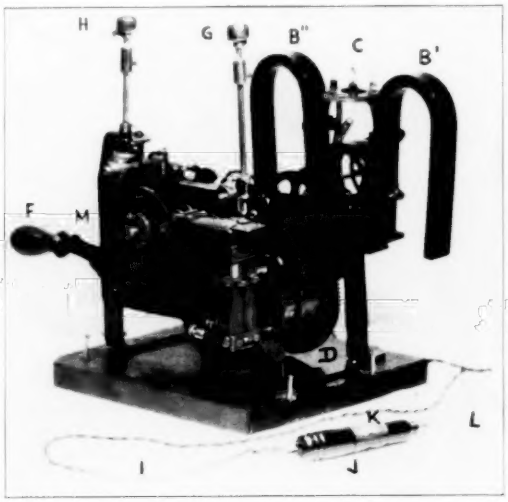


Fig. 2.—The artificial pacemaker seen from the back. The interrupter disk is shown at *M*.

determined: the lowest permitting 30 impulses per minute to be delivered, the next 60 impulses, and the highest 120 impulses. In order to demonstrate visually the production of the current and the rate at which it was being subdivided, special neon gas-filled bipolar lamps were utilized.[11] These lamps, consuming the lowest amperage of any known luminescent electric device, were activated on the negative side of the interrupter disk, and the brushes were so placed than when the current was not flowing to the outlet terminals, the lamps would glow. In other words, activation of the lamps alternated with release of the stimulating current; when the stimulating current was being delivered, the lamps were "dead."

Many highly technical and exceedingly complicated questions in pure electrophysics had to be solved before the apparatus could be successfully assembled;

11. These were furnished by the Vapor Lamp Division of the General Electric Company which has cooperated in this particular phase of the work.

it is not within the scope of this paper to enter into any of these, save to point out that the capacity effect in the heart muscle itself had to be thoroughly studied and compensated for, as did the correction for the "lag" in muscle irritability.

Photographs of the apparatus are seen in figures 1 to 4. Figure 1 shows the front aspect of the artificial pacemaker. The principal parts of the equipment (as designated in the figures) are here described:

A, magnetogenerator; note the Tesla control armature brushes.

B' and *B''*, companion magnet pieces used in building up the required magnetic flux.

C, neon lamp cluster and current indicator.

D, spring motor.

E, ballistic governor, the speed control of the spring motor.

F, handle for winding the spring motor with a ratchet arrangement to permit rewinding with the motor in action.

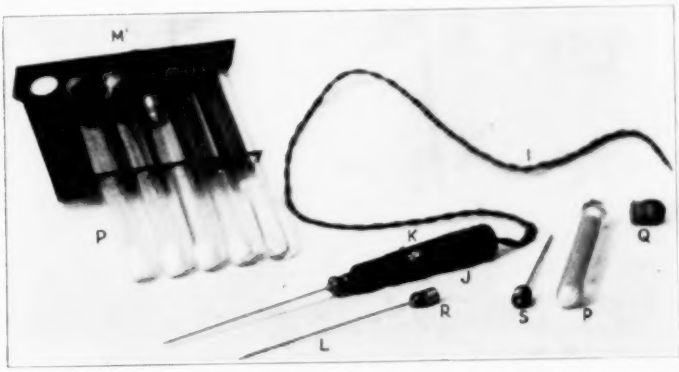


Fig. 3.—Photograph showing details of needle (*L*), its electric connections (*R*, *S*), handle (*J*) and switch (*K*). The special tube holder (*M'*) and tube (*P*) with stopper (*Q*) are also seen.

G, impulse controller for regulating the position of the interrupter brushes and giving the three positions of 30, 60 and 120 impulses per minute.

H, speed control for the spring motor, an arrangement for starting and stopping the apparatus.

I, flexible electric wires for carrying the current.

J, insulated handle.

K, switch for controlling the current to the needle.

L, needle.

A posterior view of the apparatus is shown in figure 2. Here, in addition to the foregoing, is shown one face of the interrupter disk (*M*). In figure 3 is presented clearer detail in regard to the needles, the handle and the sterile containers for the needles. The needle (*L*) is a hollow steel shaft of no. 19 gage material through which runs a highly insulated wire that terminates at the same angle as the outside needle shaft. Electric connections are shown at *R*, the outside electrode, and *S*, the inside electrode. *M'* is a tube holder containing spaces

for six tubes in which the needles are sterilized by dried heat and kept until needed. *P* represents such a tube, and *Q* is a specially prepared stopper selected for its impermeability.

For clinical use the entire apparatus is enclosed in a sturdy well built carrying case, a photograph of which is seen in figure 4. The cover *T* is held firmly down by heavy trunk catches when not in use; when open, it carries a card *O* indicating directions. The tube carrier, *M'*, is seen in its compartment; the impulse regulator is seen at *G*, while the starter control is seen at *H*. The current terminal, *N*, to which is connected the flexible cord, *I*, is indicated in its relation to the handle and needle.

The apparatus complete weighs 16 pounds (7.2 Kg.) because of the sturdy type of materials used to prevent damage in rough transportation

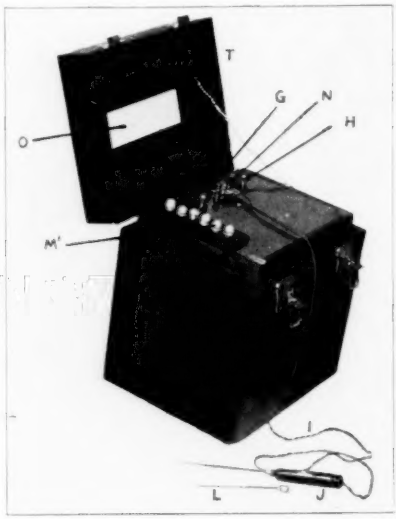


Fig. 4.—The artificial pacemaker in its carrying case.

and employment under the most adverse conditions. A laboratory model built without such protective measures weights but 8 pounds (3.6 Kg.), and it may be possible ultimately to reduce the size and weight of all models so that the apparatus can be conveniently carried in an ordinary hand bag.

EXPERIMENTS WITH THE ARTIFICIAL PACEMAKER

The successful development of the apparatus permitted its use in experimental work on laboratory animals. In November, 1929, a series of studies were made in order to determine the validity of the theories previously discussed in connection with restoration of function of the asystolic heart by controlled electric stimulus production. It soon

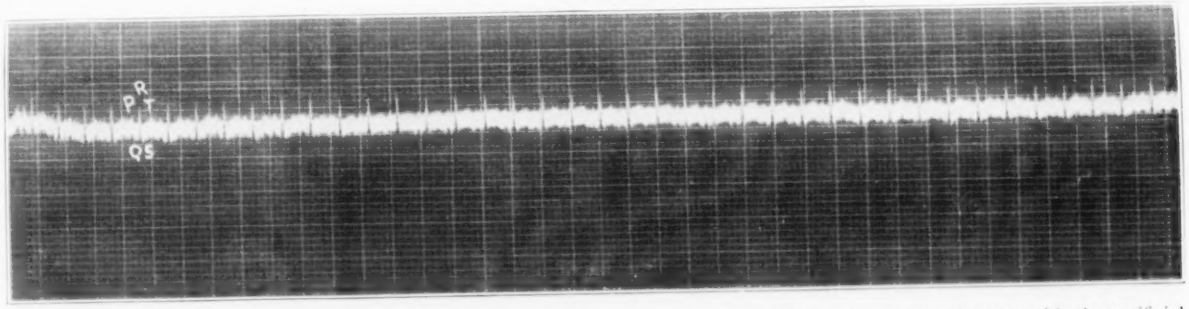


Fig. 5.—This electrocardiogram was taken before an experiment on the resuscitation of the stopped heart with the artificial pacemaker. A large healthy guinea-pig was used. There is a normal sinus rhythm with a rate of 300 beats per minute; the cardiac cycle is well defined. The P, Q-R-S and T waves are easily identified.

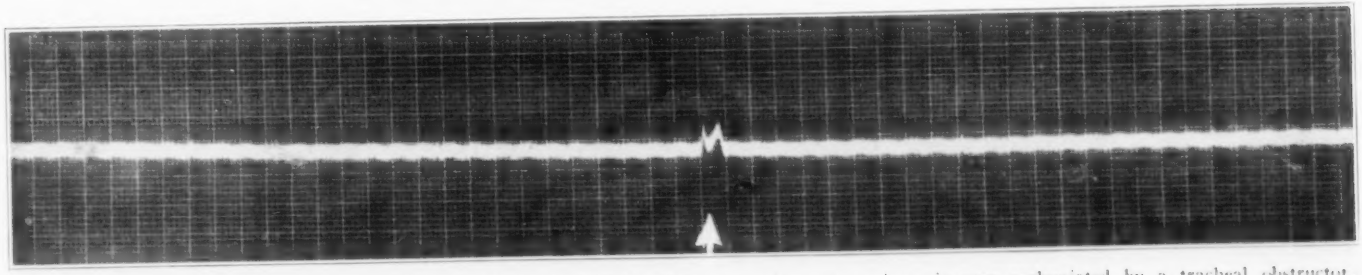


Fig. 6.—Immediately after the electrocardiographic tracings in figure 5 were taken, the guinea-pig was asphyxiated by a tracheal obstructor. Automatic respiratory movements ceased in one hundred and ten seconds, and seventy seconds later all signs of cardiac activity stopped. Exactly one hundred and twenty seconds after this the pacemaker needle was inserted into the right ventricle. This tracing, taken as lead II, shows complete cardiac arrest; the point marked by the arrow indicates insertion of the needle. It is accompanied by a ventricular extrasystole.

became evident that the type of needle used was of extreme importance and that the reasons for previous failures to resuscitate the heart by electric stimulation were due to the fact that *the entire heart was involved in the electric circuit.* In such cases the heart is unable to respond according to its normal mechanism, and the sequence of events in the cardiac cycle is considerably disturbed. When large differences of potential are used, the heart may go into fibrillation and all the phenomena found in electrocution are discovered.[12]

When, on the other hand, the electric stimulus enters the heart over a very small segment, this area becomes a focus from which the normal stimulus can pass through the heart over its customary pathways. From a theoretical point of view the closer the two electrodes carrying the stimulating current can be approximated, the nearer will this artificial focus approach that seen in the normal functioning organ. Of fundamental importance is the difference in the basic theories between the previous modes of electrically stimulating the heart and that concerned with artificial pacemaker methods. In the former, the electric current introduced into the heart is the *same current that is supposed to cause contraction of the heart muscle tissue,* whereas in the latter theory the introduced electric impulse serves no other purpose than to provide a controllable *irritabile point from which a wave of excitation may arise normally and sweep over the heart along its accustomed pathways.*

In other words, the artificial pacemaker produces the same effect as that previously discussed in regard to the mechanical prick of an injecting needle; we have seen that in the latter condition the point of irritability that arises in the anoxemic myocardium generates its own excitation wave and that it is followed by certain well conditioned physiologic responses. The artificial pacemaker method proceeds one step further, while the needle prick alone gives only one opportunity for stimulus production, the rhythmically controlled artificial pacemaker permits many such stimuli to be applied over a period of time sufficiently long to enhance the probability of the renewal of automatic cardiac activity.

The practical use of the artificial pacemaker method of restoring the automatic activity of the stopped heart can, perhaps, be no better visualized than by the following experiments.

A large guinea-pig was "killed" by mechanical asphyxiation, a tracheal obstructor of the Porter type being used. When all respiratory movements had been stopped and no heart sounds could be determined, electrocardiographic tracings were made with the animal in the position of lead II (right foreleg and left hind leg). Figure 5 is the electrocardiogram taken prior to the experiment; the individual P, R and T waves are easily identified. Figure 6 was taken one hundred and twenty seconds after all evidences of cardiac activity had ceased; the

12. Hooker, D. R.: Am. J. Physiol. **91**:305 (Dec.) 1929.

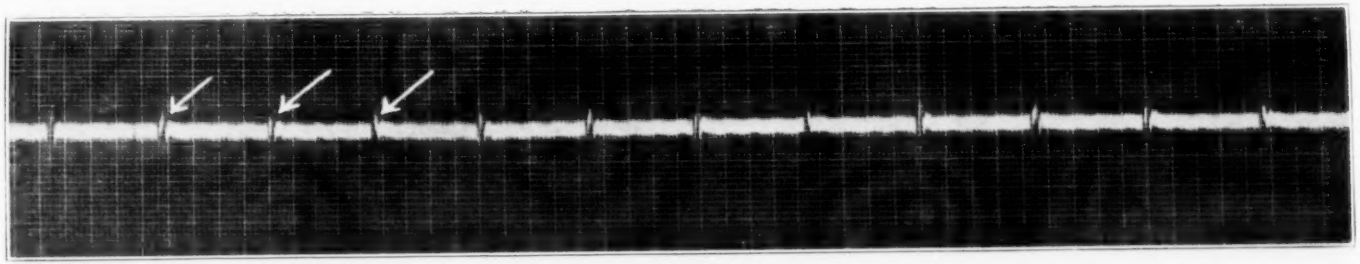


Fig. 7.—No further extrasystoles having developed within thirty seconds, the artificial pacemaker was started; a model BCM instrument was used. The rotor speed was set at 64 beats per minute. Note the periodic diphasic current occurring in the tracing.

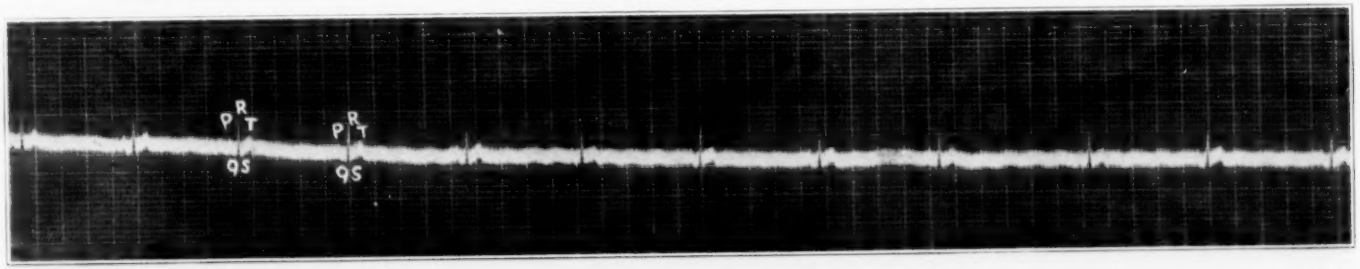


Fig. 8.—At the end of sixty seconds the artificial pacemaker was stopped and the needle withdrawn. Note the return of automatic cardiac activity with normal electrocardiographic waves, the P, Q-R-S and T waves being identical with those seen in figure 5. Of special interest is the rate; it is synchronous with the artificial pacemaker pulsations as seen in figure 7.

graph shows a straight line with certain extracardiac currents which cannot be removed without dampening the entire curve. These currents are constant and can be disregarded. At the point indicated by the arrow, a pacemaker needle was inserted high up in the right ventricle and an extrasystole promptly developed, but was not followed by any further signs of myocardial activity, the heart apparently being in the second phase of anoxemia.

After thirty seconds the artificial pacemaker current was started, and in figure 7 is shown the graphic tracings of the current effects in the anoxemic heart muscle. The pulsations are readily seen to be regular at a rate of about 60 to 64 per minute. At the end of sixty seconds the pacemaker was stopped and the needle rapidly withdrawn; electrocardiographic tracings (fig. 8) were taken and an especially interesting phenomenon was discovered. Normal sinus beats with readily recognized P, R and T waves were found to be developing at *exactly* the same rate as the previously developed artificial pacemaker ratio. This rhythm continued for about forty seconds, after which the normal sinus rate reestablished itself. In figure 9 is shown the return to a rate slightly faster than that seen before the experiment.

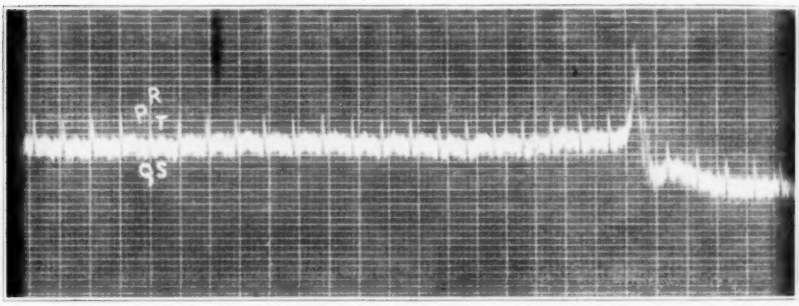


Fig. 9.—Return to normal sinus rhythm after forty seconds of restored cardiac activity; the rate is now slightly faster than that seen in figure 5 at the beginning of the experiment.

This experiment was repeated many times on other guinea-pigs, rabbits and one large dog, different modes of producing cardiac standstill being employed. It was soon found that whereas the current delivered by the artificial pacemaker had been calculated to meet the needs of the human heart, the stimulus produced in small animals was at times excessive in that widespread myocardial activity occurred much in the same fashion as that already discussed in connection with the older methods of resuscitating the stopped heart. For this reason, certain resistance units were added to the circuit when smaller animals were being used.

In figure 10 is shown an experiment carried on with a large guinea-pig when the pacemaker current was not dampened. The graphic records are interesting in confirming the theory of greater myocardial involvement when stronger currents are used. Figure 10 shows the record of the asystolic heart taken in lead II. Figure 10*B* demonstrates myocardial activity during the introduction of the

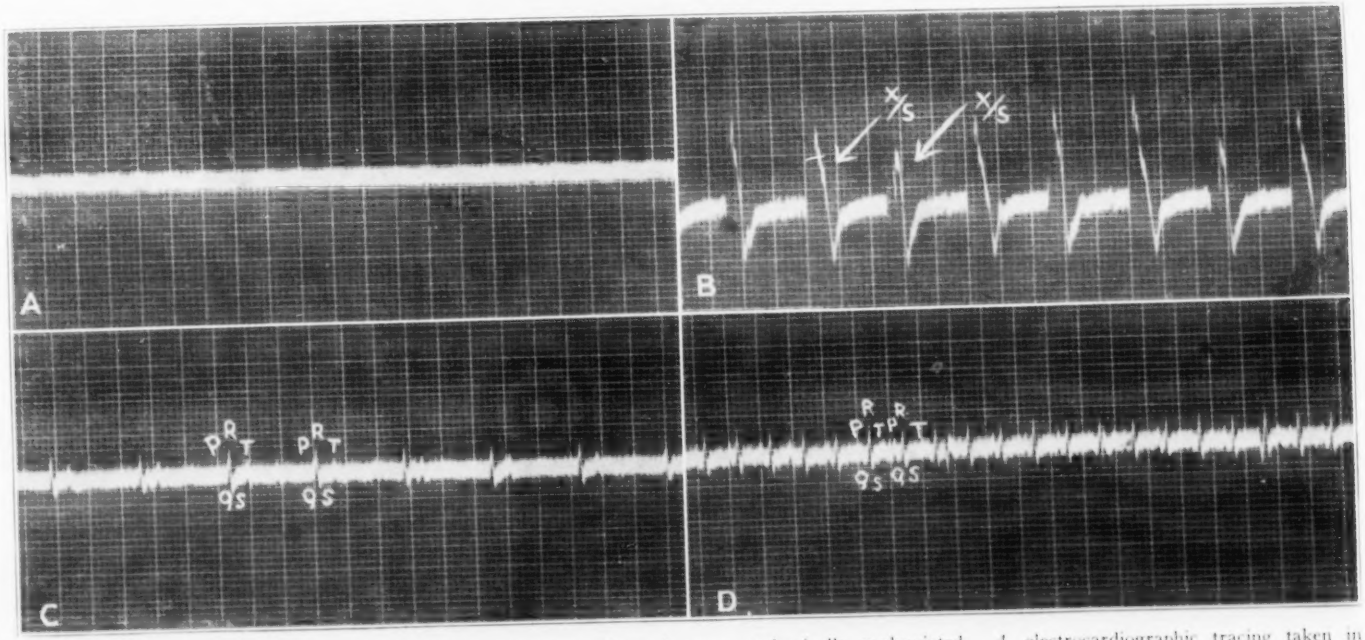


Fig. 10.—Resuscitation of the asystolic heart. A large guinea-pig was mechanically asphyxiated. *A*, electrocardiographic tracing taken in lead II, during the period of cardiac standstill. *B*, about forty seconds later, undampened pacemaker stimuli were released in the right ventricle at the rate of 120 per minute. Note the bizarre type of right ventricular extrasystoles that developed. *C*, removal of the pacemaker needle was followed by a normal sinus rhythm corresponding in rate with that established by the artificial pacemaker. *D*, restoration to regular normal sinus rate and rhythm, the pacemaker of the heart now having taken over control of the cardiac cycle.

stimulating current; the complex takes the form of a bizarre right ventricular extrasystole, the pacemaker needle apparently being nearer the base of the right ventricle than in the right auricle where it was directed. In figure 10*C* is disclosed a regular rhythm with the same rate as that developed by the artificial pacemaker. This rhythm continued for about one minute, when there was a sudden return to regular sinus rhythm (fig. 10*D*).

From a purely laboratory point of view many interesting problems arise which are worthy of further study; one of the most important of these is an inquiry into the factors responsible for the return of sinus rhythm at exactly the same rate as that produced experimentally by the artificial pacemaker. In the initial stage of the restoration mechanism, the renewal of automatic cardiac activity seems to start at the same rate as that of stimulus release by the artificial pacemaker. Apparently rhythmic changes develop in the myocardium as a result of this impulse release and the sinus node seizes on these alterations as the first step back to its own rhythmic rate. Unquestionably, the problem is more complicated than this simple theory would indicate, and many factors not here considered may be responsible for this transitional step. In discussing this feature with physiologists we have been accustomed to employ the simile of the normal pacemaker "following in the footsteps of the artificial pacemaker until the former had recovered its equilibrium and could enter upon its own initiatory phenomena."

Experimental evidence in support of the theory of increasing anoxemia resulting in the breakdown of electrodynamic factors is graphically demonstrated in the following study.

In this case a rabbit was anesthetized until cardiac standstill had taken place. Figure 11*A* shows electrocardiographic tracings in lead III (left foreleg and left hindleg) taken about ten minutes after the animal was pronounced dead. An undampened pacemaker current at 60 impulses a minute was introduced into the right ventricle, and figure 11*B* shows the type of right ventricular extrasystoles that developed as a result of this experiment. The artificial pacemaker was run for ten minutes, electrocardiograms being taken from time to time. Two features of interest are apparent: the first is the alternating fatigue phenomenon of Winterberg seen in figure 11*C*, where every other extrasystole is becoming smaller. The second is the attempt at automatic renewal of the pacemaker. Small P waves being seen at a rate of 160 per minute. They are apparently unable to initiate a ventricular response because of the greater stimulus introduced by the pacemaker current.

In contrast to this phenomenon is that seen in figure 12, when the pacemaker needle has been introduced into the left ventricle of the normally beating heart. In this experiment, a guinea-pig was etherized and an artificial pacemaker current at the rate of 60 impulses per minute was introduced. The graph shows the normal sinus rhythm of 300 beats per minute, interrupted 60 times a minute by the introduced stimulus current. Each stimulus is followed by a left ventricular extrasystole whenever it does not meet the refractory phase of the cardiac cycle.[13]

13. Parsonnet, A. E., and Hyman, Albert S.: Applied Electrocardiography, New York, The Macmillan Company, 1929, p. 90.

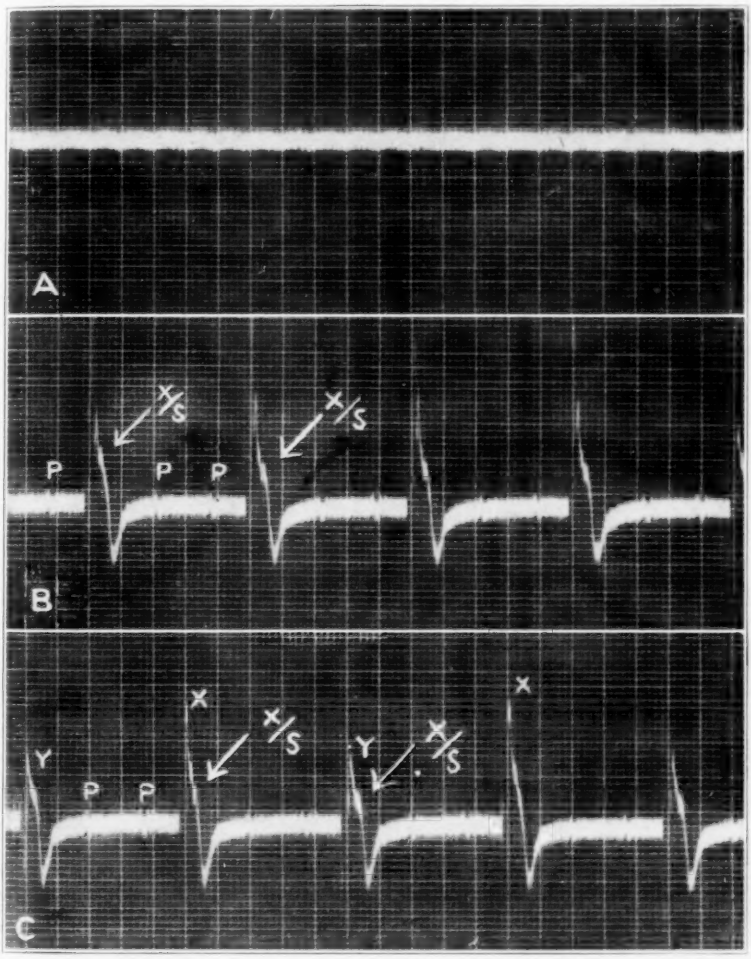


Fig. 11.—Experiment showing the effect of prolonged excitation from undampened artificial pacemaker stimuli. *A*, electrocardiographic tracing taken in lead III of the asystolic heart. *B*, undampened artificial pacemaker stimuli released in the right ventricle at the rate of 60 per minute. Note the development of auricular beats (P waves). *C*, tracings taken after ten minutes of artificial pacemaker control. Note the alternating fatigue phenomenon of Winterberg (*X*, large response; *Y*, small response).

The normal activity of the heart is apparently but slightly embarrassed by the artificial pacemaker current. The importance of this phase of the problem cannot be overemphasized, as the criticism has sometimes been made that the heart may actually be beating in certain patients who have been pronounced dead; in such persons it was thought that the introduction of the artificial pacemaker current might do damage to the cardiac mechanism. Apparently when the heart is contracting in response to its own stimulus production, the introduction of an irritable focus results in a response no wise different from that seen in the extrasystolic arrhythmias.

In the domain of pure scientific research, the artificial pacemaker opens avenues of approach to many problems in cardiovascular physiologic pathology; only two of these can be presented here. The suggestion was made by Dr. A. E. Parsonnet that the artificial pacemaker might find a place in those cardiovascular disturbances which are clinically manifested by such gross irregularity of the circulation that death occurs. He had especially in mind those types of very rapid auricular fibrillation which are associated with low threshold values of the junctional and bundle tissues of the heart; in such instances the ventricular rate is also very rapid, reaching as high as from 180 to 220 irregular contractions per minute. The peripheral circulation is thus reduced to hazardously low levels, and stasis phenomena may develop.[14] With a pacemaker needle inserted in one or the other ventricle, it was thought that the ventricular rate might be controlled by this means when all other types of therapy had failed.

Paroxysmal tachycardia is another type of irregularity that not infrequently tests the skill of the clinician; responses to the ordinary modes of therapy are, as a rule, futile. When the focus of the new rhythm lies in the nodal area, vagal stimulation may interrupt the tachycardia and the return to a normal rate is prompt. More often, however, the ectopic focus lies in the ventricles, auricles or the Tawara nodal tissue; drug therapy in these cases is always disappointing. As the rhythm is extrasystolic in origin it should obey the Herring law of maximal stimulation of muscle segments; the artificial pacemaker in such a case would release a stronger stimulus for contraction than the ectopic focus, and it would thus control the rhythm of the heart. Starting at a relatively high rate, say 160 or 180 impulses per minute, when control had been secured the normal rate could assert itself again. The employment of the artificial pacemaker in such disturbances of rhythm enters into other fields not immediately associated with the question of resuscitation of the stopped heart; it is mentioned here only to suggest profitable lines of inquiry made available by this type of apparatus.

14. Hyman, Albert S.: Am. J. Pub. Health **19**:1103 (Oct.) 1929.

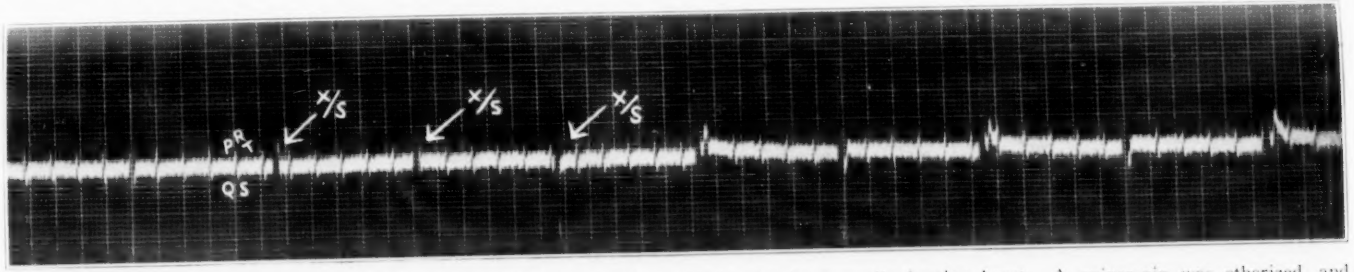


Fig. 12.—Experiment showing the effect of the artificial pacemaker stimulus in the normally beating heart. A guinea-pig was etherized, and electrocardiographic tracings were taken; the normal pacemaker is controlling the cardiac cycle with a rate of about 300 per minute. The artificial pacemaker is releasing its impulse at a rate of 60; each impulse is followed by a left ventricular extrasystole whenever the time relations are such as to permit ventricular response. Note that when the normal pacemaker and the artificial pacemaker are operating simultaneously the effect of the latter is the production of a regular extrasystolic arrhythmia.

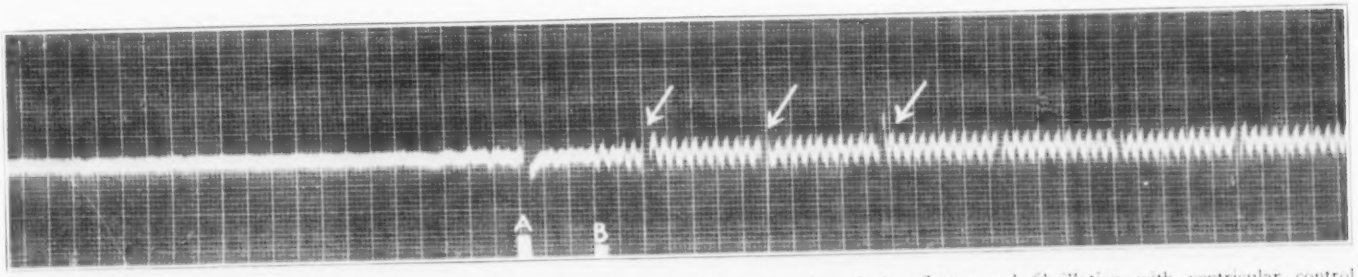


Fig. 13.—Electrocardiographic tracing (lead II) showing experimentally produced auricular flutter and fibrillation with ventricular control maintained by impulses from the artificial pacemaker. At point *A*, faradic stimulation of the auricles at a rate of about 900 per minute was begun, while at point *B* the artificial pacemaker with an impulse release of 60 was started.

In figure 13 is shown a rabbit heart made asystolic by mechanical asphyxiation. At point *A*, the artificial pacemaker current at a rate of about 60 impulses per minute was introduced, and at point *B* a faradic stimulating current was applied to the exposed right auricle at a rate of about 900 impulses per minute. The graph shows ventricular rhythm maintained at a rate of 60, while the auricular rate is very rapid, at the rate of about 900. Figure 14 was taken four minutes later. The auricles are apparently not responding as rhythmically as at the beginning of the experiment. At point *C* this faradic current was stopped, but the pacemaker current was continued, the ventricles still responding regularly. These graphs are introduced merely to point out the wide field of applicability made possible by the artificial pacemaker.

THE CLINICAL USE OF THE ARTIFICIAL PACEMAKER

Sufficient evidence having been obtained from investigations on laboratory animals, the practical use of the theory and apparatus finally awaited trial in actual clinical fields. Having demonstrated that the insertion of a needle electrode carrying a rhythmic stimulus apparently caused no more harm to the normal heart than that of any other injecting needle and also having proved that such a rhythmically introduced current may carry on the rôle of the pacemaker of the heart until the normal pacemaker is able to reestablish itself, it was decided to use the method at first only on patients who had been pronounced dead and in whom all other methods of resuscitation had failed. The cooperation of clinicians interested in the problem was readily secured, once their objections to the possibility of the heart becoming "electrocuted" by this method was overcome.

The prejudice against intracardiac injection has long given way to the full acceptance of such therapy even before actual death has supervened. When the patient has "died," such objections as may still fill the mind of the medical attendant ordinarily disappear, the feeling being that no harm can come to the patient, and at the same time the possibility of resuscitation is always present. The use of the artificial pacemaker, radical as the procedure first appeared to some, soon gave way to a full acceptance of its use, and although the number of patients successfully treated by this method is still very small, a more or less widespread adoption of the method would unquestionably show the validity of the procedure.

It is hoped that with the publication of this work the method will come into greater general use and that a large series of figures may be obtained in order to give a true estimation of the value of the procedure. The histories of cases are not recorded here, but such satisfactory results have been obtained that the feeling has been that while the arti-

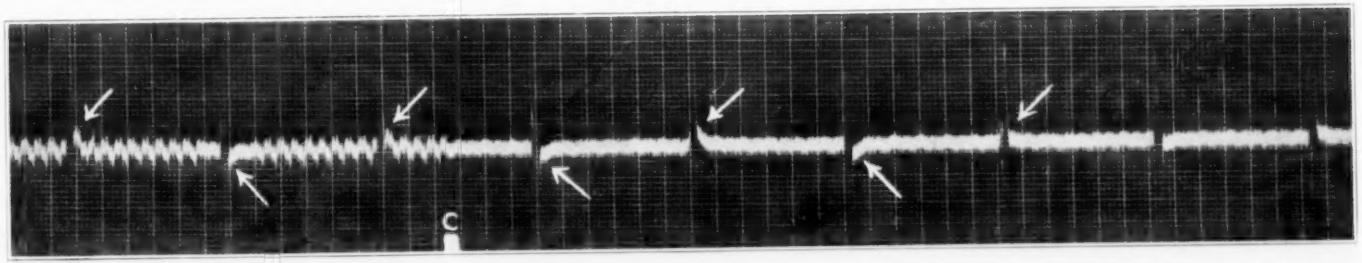


Fig. 14.—The same experiment four minutes later. At point C, the faradic stimulation of the auricles was stopped, but the pacemaker impulses were continued. Note the gradual disappearance of alternate ventricular lag.

ficial pacemaker finds its greatest value in the resuscitation of the normal asystolic heart which has been stopped by the many causes previously enumerated, it also finds a place in the attempt to reestablish cardiac activity in those who have succumbed to death by other causes. The method is as yet too new to draw any hard and fast rules in regard to its uses, but its relative harmlessness in contrast to the favorable results to be anticipated recommends this type of resuscitation in all cases when the usual methods have proved futile. Even the saving of one life is sufficient to place the artificial pacemaker among those procedures now so eagerly seized when the emergency occurs.

SUMMARY

1. Stimulation of the stopped heart by electrical methods has previously failed because most investigators have attempted to reactivate the heart by neurogenic excitation.

2. When electric current has been applied directly to the heart, it has been done by placing the entire organ in the electric circuit; the result has been that the heart is unable to maintain its normal cycle. When strong currents have been used the factors discovered in electrocution are seen to be present.

3. In using a clinical needle through which is carried an electric impulse, and in having the two electrodes so close together that only a small pathway is concerned in the electric arc established by the heart muscle, an irritable point is produced.

4. This irritable point becomes the focus from which an excitation wave may spread over the heart muscle, the excitation wave developing and spreading according to normal physiologic conditions. The impulse released from the pacemaker needle differs in no way from that produced by the prick of any injecting needle except that in the latter instance only one stimulus is developed, while in the former any number can be delivered to the heart muscle.

5. An apparatus has been constructed which attempts to simulate the excitation wave developed by the normal sinus nodal pacemaker; it consists in a special current generated by a magneto which is activated by a spring motor, making it instantaneously available at any time, at any place and under all circumstances, as it is an independent electric unit. The current from this generator can be so regulated that the impulses are delivered to the needle point at a constant regular rate varying from 30 to 120 beats per minute.

6. The needles are carried in hermetically sealed tubes that have been sterilized; in the puncture procedure the same aseptic precautions must be observed as in any other sterile injecting manipulation. The

needle is inserted into an insulated handle which carries the terminals of the electric circuit from the generator. A convenient switch on the handle permits the current to be introduced into the needle at will.

7. Experimental animal studies have shown that the arrested heart is rapidly returned to automatic sinus activity after the response to the artificial pacemaker has restored some of the normal circulatory balance. Typical graphs are presented which show the electrocardiographic exposition of the events that take place in the heart when the artificial pacemaker is applied to the stopped heart.

8. The use of the artificial pacemaker in the normally beating heart is also shown, and the relative harmlessness of the procedure is indicated, the result being the development of a regular extrasystolic arrhythmia. The artificial pacemaker impulse is followed by an ectopic beat from that area of the heart stimulated.

9. The question of utilizing the artificial pacemaker in certain gross irregularities of the heart is also discussed, but this field still requires considerable investigation before conclusions of any type can be considered.

10. In view of the possible advantageous results to be anticipated by the use of the artificial pacemaker in the arrested heart which does not respond to the usual methods of therapy, the employment of this method is suggested. When patients have succumbed to disease processes, an attempt can be made to renew automatic cardiac activity by the use of the artificial pacemaker without in any way jeopardizing their condition.

11. When correctly used, the artificial pacemaker may prove to be of inestimable value in the restoration of those patients now succumbing to cardiac arrest; employed together with other established life-saving procedures it may well be included in every physician's armamentarium against the final struggle with death.

FIBROMYOMA OF THE UTERUS, CARDIAC FAILURE, ANEMIA AND EDEMA

REPORT OF A CASE

H. BRANDMAN, M.D.
CHICAGO

The fact that heart disease is associated with fibromyoma of the uterus is well known. The discussions of this association introduced by Hoffmeir [1] and continued by some of the early authors—Leopold,[2] Fehling,[3] Brosin,[4] Hennig,[5] Landau,[2] Kessler,[6] Wilson,[7] Doran,[8] Chavanez [9] and others—still continues. The more extensive and thorough work of later investigators—Boldt,[10] Healy,[11] Garkisch,[12] Strassmann and Lehmann,[13] Kelly and Cullen [14] and Janaki [15]—points to a frequency of simultaneous occurrence of the two conditions ranging from 20 to 40 per cent. Such a high figure does not seem to apply to carcinoma or

From the Department of Medicine of the University of Chicago.

1. Hoffmeir: Ueber Erkrankungen der Circulatsorgane bei Unterleibsgeschwülsten, Ztschr. f. Geburtsh. u. Gynäk. **11**:366, 1885.

2. Cited by Albrecht, H., in Halban and Seitz: Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenberg, 1928, vol. 4, p. 415.

3. Fehling: Beiträge zur operativen Behandlung der Uterus Myome, Zentralbl. f. Gynäk. **18**:276, 1887.

4. Brosin: Zentralbl. f. Gynäk. **18**:96, 1887.

5. Hennig, C.: Die Beweise für den Wechselverkehr zwischen Herz und Gebärmutter, Ztschr. f. Geburtsh. u. Gynäk. **29**:131, 1894.

6. Kessler, cited in Am. J. Obst. & Gynec. **46**:417 (Sept.) 1902.

7. Wilson, T.: The Cardiopathy of Uterine Fibromyoma, J. Obst. & Gynæc. Brit. Emp. **6**:107 (Aug.) 1904.

8. Doran, A.: Fibroids and Heart Disease, J. Obst. & Gynæc. Brit. Emp. **3**:13 (Jan.) 1903.

9. Cited by Cumiston, C. G.: Cardiac Disease and Uterine Fibromata, New York State J. Med. **82**:893, 1905.

10. Boldt, H. J.: Uterine Myofibromata and Visceral Degeneration, New York State J. Med. **82**:887 (Oct.) 1905.

11. Healy, W. P.: Fibromyoma Uteri, New York State J. Med. **97**:922 (May 3) 1913.

12. Garkisch, A.: Klinische nud anatomische Beiträge zur Lehre von Uterus Myom, Berlin, S. Karger, 1910, p. 9.

13. Strassmann and Lehmann: Zur Pathologie der Myomerkrankungen, Ztschr. f. Geburtsh. u. Gynäk. **38**:111, 1898.

14. Kelly, H. A., and Cullen, T. S.: Myomata of the Uterus, Philadelphia, W. B. Saunders Company, 1909, p. 451.

15. Janaki, J.: Herz Veränderungen bei Myom, Zentralbl. f. Gynäk. **83**:2589, 1922.

other diseases of the uterus or its appendages. This statistical concomitance has warranted the belief on the part of some gynecologists and internists that the new growth can specifically or uniquely injure the heart. Hoffmeir,[1] Brosin,[4] Strassmann and Lehmann,[13] von Lingen,[16] Hennig,[5] von Müller [17] and others stated this opinion. On the other hand, some authors have denied this relationship. Severe critics of the hypothesis that fibromyoma is a specific danger to the heart are Winter,[18] McGlinn,[19] Martin,[20] Wilson,[7] Romberg,[21] Krehl,[2] von Jaschke [22] and Walthard.[23] Winter was the first clinician and McGlinn the first pathologist to emphasize sharply the lack of critical judgment of some authors and the incomplete and inadequate study of patients supposedly having "Myom-Herz." The former, also, called attention to the fact that such studies should represent the joint efforts and responsibilities of various specialists and not rest entirely on the shoulders of the gynecologist.

Some clinicians—Fleck,[24] Neu,[25] Herz,[26] Mahler,[27] Strumpell,[3] Aschner,[2] Freund [2] and Romberg [21]—conceived the new growth to be a focus or part of a group of phenomena relating to the disturbance of the endocrine glands. It was thought, for example, that the fibromyoma acted on the heart as does the thyroid gland in thyrotoxicosis, or that it was a passive or active agent in a general disease more manifested

16. von Lingen, E.: Ueber die Beziehungen zwischen Uterus Fibrom und Herz, Ztschr. f. Geburtsh. u. Gynäk. **66**:654, 1904.

17. von Müller, F.: Die Bedeutung des Blutdrucks für den praktischen Arzt, München. med. Wchnschr. **70**:1 (Jan. 5) 1923.

18. Winter, G. W.: Myom und Herz, Ztschr. f. Geburtsh. u. Gynäk. **87**:225, 1924.

19. McGlinn, J. A.: Fibroid Tumors of the Uterus, Surg., Gynec. & Obst. **18**:180 (Feb.) 1914; The Heart in Fibroid Tumors of the Uterus, Tr. Am. Obst. Soc. **38**:481, 1913.

20. Martin, in discussion of Strassmann and Lehmann (footnote 13).

21. Romberg, E.: Lehrbuch der Krankheiten des Herzens und der Blutgefässe, ed. 4, Stuttgart, F. Enke, 1925, pp. 99, 242, 248 and 500.

22. von Jaschke, in Frankl-Hochwart, L.: Die Erkrankungen des weiblichen Genitales im Beziehungen zur inneren Medizin, Vienna, Alfred Holder, 1913, vol. 1, p. 58.

23. Walthard, M., in Menge and Opitz: Handbuch der Frauenheilkunde, ed. 1, Wiesbaden, J. F. Bergmann, 1913, p. 170.

24. Fleck, G.: Myom und Herzerkrankungen in ihren genetischen Beziehungen, Arch. f. Gynäk. **71**:258, 1904.

25. Neu: Experimentalles und anatomisches zur Frage des sogenannte Myomherz, Zentralbl. f. Gynäk. **2**:1532, 1911.

26. Herz, M.: Kropfherz, Myomherz, Klimakterium, Wien. med. Wchnschr. **22**:517, 1913.

27. Mahler, J.: Myomherz und tiefen Therapie, Med. Klin. **14**:588, 1914.

in the cardiovascular system. E. Strassmann [28] expressed the belief that some deleterious agent acted on the uterus to produce the tumor and on the heart and blood vessels to cause fibroid, fatty and other damaging changes in the heart muscle and the hypertensive state. Still others implicated the ovaries as the cause of the picture of disturbed action of the heart.

Von Müller [17] thought that such uterine disease could initiate and propagate the hypertensive state found in the later decades, but no other authorities seem to have agreed with this view. Polak, Mittel and McGrath,[29] in a study of blood pressures in patients with fibromyoma of the uterus, could not demonstrate that hypertension was definitely related to the occurrence of the neoplasm.

The question of whether the tumor itself can produce substances harmful to the heart has been investigated by Thalheim and Birnbaum [30] with chemical methods and by Patta and Decio [31] with injections of extracts of the fibroids into animals. No definite conclusions accrued.

Other beliefs, now more or less ignored, were that the tumor does harm by compressing blood vessels, ureters and other abdominal structures, by impeding the flow of blood through the uterus, by pressing on the sympathetic plexuses and indirectly by producing pain. Uncommon occurrences such as encroachment on the position and movements of the diaphragm and massive degenerations of fibroids have to be admitted as real, though secondary, causes of disturbance of the heart.

Though a direct cause and effect relationship has not been demonstrated, there exist mechanisms, secondary in initiation and nature, that can more or less readily be held to account for the existence of heart disease in patients with fibromyoma of the uterus. Prominent among them is anemia caused by repeated uterine hemorrhages, at or between the menstrual periods and thus conditioned by the tumor. The anemia, by virtue of its damaging influence on the heart muscle, could bring about cardiac failure. This is truly a secondary effect, as it can be observed in other forms of hemorrhage. This view of the mechanism of myocardial insufficiency is advocated by Winter,[5] Kelly and Cullen.[14]

28. Strassmann, E.: Die Kreislaufänderung durch Klimakterium und Kastration bei Myom, Arch. f. Gynäk. **126**:169, 1925.

29. Polak, J. O.; Mittel, E. A., and McGrath, A. B.: What Is the Relationship of Hypertension to Fibroid Tumor of the Uterus? Am. J. Obst. & Gynec. **4**:227 (Sept.) 1922.

30. Thalheim and Birnbaum: Untersuchungen über die chemische Zusammensetzung der Myome und der Uterus Muskulatur, Monatschr. f. Geburtsh. u. Gynäk. **28**:510, 1908.

31. Patta, A., and Decio, C.: Ueber die Beziehung des Uterusmyom und Kreislauf, Monatschr. f. Geburtsh. u. Gynäk. **34**:548, 1911.

Walthard,[23] McGlinn,[19] Healy,[11] Engelmann,[32] Martin [20] and Romberg.[21] It is also the one most frequently presented in current textbooks of gynecology and internal medicine.[33]

In the case of a patient presenting severe anemia and heart failure, an occasion was afforded to test clinically the truth of the assumption of the injury of the heart by anemia. The patient was studied with more than the usual care in ordinary hospital observation; frequent hematologic studies (red and white blood cell counts and estimations of hemoglobin), chemical determination of the blood (essentially plasma protein and urea) and electrocardiographic and teleoroentgenographic studies were made. Figures 1 and 2 show the alterations observed with the aid of these methods. The whole course of observation covered a period of about thirteen months and includes, besides the preliminary hospitalization, a number of return visits for complete reexamination.

REPORT OF A CASE

History.—Mrs. C. V., aged 39, a housewife, was first seen on Aug. 10, 1930, at the Albert Merrit Billings Hospital. The family, childhood and other past history was unimportant. Two years previous to admission, there was a left peritonsillar abscess of ten days' duration. She had had three normal pregnancies and deliveries. The third, eight years previously, seemed to mark the beginning of the present illness. The menstrual process, which was normal before the onset of pregnancy, was accompanied by a progressively increasing amount of bleeding at each period, and within the month before admission to the hospital, by gushes of blood from the vagina with each effort of defecation. At the later periods, it was estimated that as much as a pint of blood was lost. The course was one of progressive invalidism, consisting of breathlessness, sensations of pounding and pain in the left anterior thoracic region and consciousness of rapid beating of the heart. Formerly these came with the slightest exertion, but in the three days before admission they occurred spontaneously and were severe enough to require absolute confinement in bed. Furthermore, there was persistent and increasing swelling of the legs, eyelids and right arm.

32. Engelmann: Beobachtungen über Myome der Gebärmutter, Arch. f. Gynäk. **76**:133, 1905.

33. Graves, W. P.: Gynecology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 143. Miller, C. J.: An Introduction to Gynecology, ed. 1, St. Louis, C. V. Mosby Company, 1931, p. 194. Lynch, F. A., and Maxwell, A. P.: Pelvic Neoplasms (Gynecologic and Obstetrical Monographs), New York, D. Appleton and Company, 1931, vol. 10, p. 100. Anspach, B. M.: Gynecology, Philadelphia, J. B. Lippincott Company, 1927, p. 302. Kulbs, F., in Mohr and Staehlin: Handbuch der inneren Medizin, Berlin, Julius Springer, 1928, vol. 4, p. 581. Curtis, A. H.: A Text-Book of Gynecology, Philadelphia, W. B. Saunders Company, 1931, p. 72. Crossen, H. S.: Diseases of Women, ed. 7, St. Louis, C. V. Mosby Company, 1930, p. 572. Vaquez, H.: Diseases of the Heart, translated by G. F. Laidlaw, ed. 1, Philadelphia, W. B. Saunders Company, 1924, p. 451. Special mention of the excellence of the discussion of the association of heart disease and fibromyoma of the uterus by H. Albrecht (footnote 2) should be made here.

As far back as the onset, the patient had been informed of having anemia and had received frequent intravenous injections of solutions of ferrous salts, without relief.

Examination.—When first seen, the patient was sitting upright in bed and breathing rapidly and with effort. An extensive edema, principally in the soft

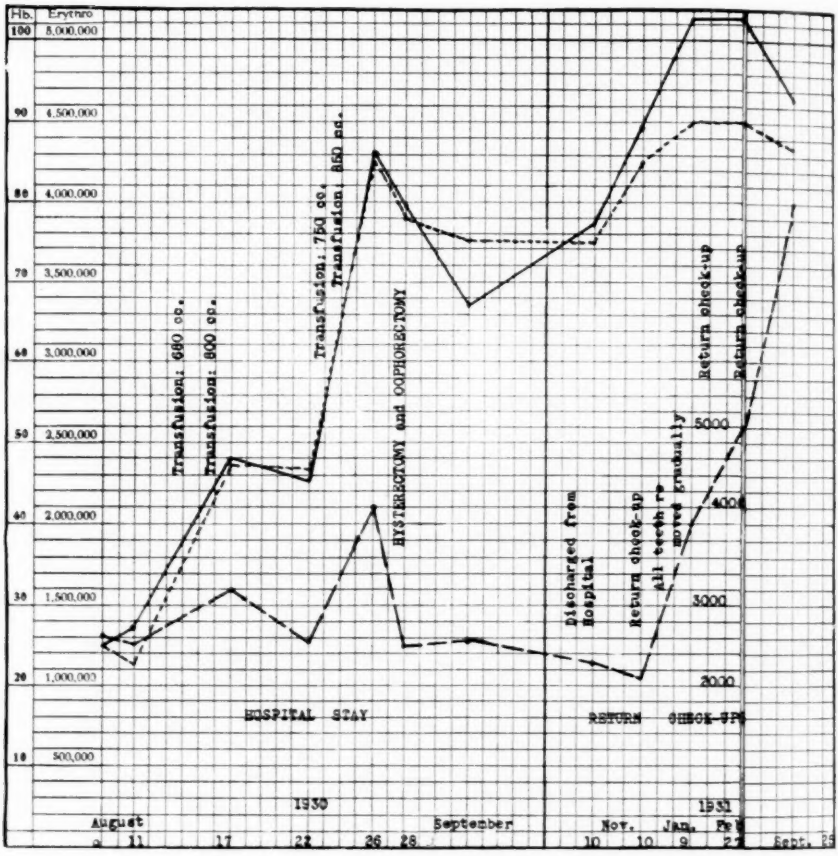


Fig. 1.—Chart showing relationships between red and white blood cell counts and percentage of hemoglobin and transfusions. The short dash line indicates hemoglobin in per cent; the continuous line, the red cell count in millions, and the long dash line, the white cell count in thousands.

tissues of the face, the right arm and the lower part of the back and legs was present. There were marked gingival exudation and dental caries.

Examination of the chest showed dulness to percussion over the base of the right lung and corresponding regional suppression of breath sounds, with crepitant

and moderately coarse râles. The maximum apex impulse was diffuse, and was felt in the anterior part of the left axilla in the fifth interspace. A loud, rough, systolic murmur was heard constantly over the region of the maximum apex impulse. The blood pressure was 160 mm. of mercury systolic and 80 diastolic. Abdominal palpation revealed a firm, tender, nodular and somewhat fixed ovoid

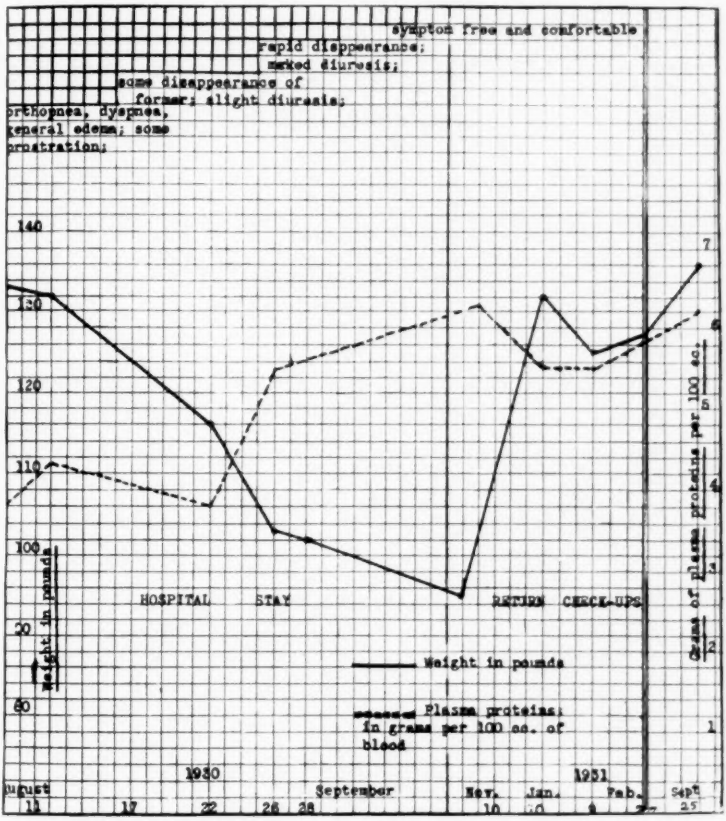


Fig. 2.—Chart showing relationship between weight and plasma proteins and the variation in certain symptoms. The blocks indicate the severity of the symptoms.

mass projecting 10 cm. above the symphysis of the pubis in the midline. Pelvic examination demonstrated the mass to be a part of the uterus.

Marked secondary anemia and leukopenia (changes in the hematologic observations during the course of the illness are shown in fig. 1), albuminous urine of low concentration, a diminished amount of plasma protein and low concentrating power of the kidneys (as measured by the ability to clear the blood of urea) were

found in the first laboratory examinations. According to a teleoroentgenogram the heart was greatly and generally oversize, with a configuration suggestive of mitral stenosis. The waves of the electrocardiogram were of low amplitude. (The teleoroentgenograms and electrocardiograms are shown in figure 3.)

The temperature before operation varied between 99 and 101 F., but occasionally it was as high as 102.5 F. The pulse rate usually varied from 90 to 140, and the respiratory rate, from 22 to 40. All three varied almost directly with the degree of the symptoms and signs described.

Diagnosis.—A diagnosis was made of large, bleeding and possibly infected fibromyoma of the uterus, mitral stenosis with myocardial hypertrophy and dilatation, severe anemia, generalized edema (including right hydrothorax) and severe oral sepsis. Chronic glomerulonephritis, active endocarditis and general sepsis were also considered.

On August 14, 16, 23 and 24, 680, 800, 750 and 850 cc. of blood were transfused into the patient by the citrate method, with practically no ill effects, except one short chill. By August 17, the difficulty in breathing and other discomfort had disappeared. The edema, as indicated by the weight and physical findings (fig. 2), was rapidly disappearing. Diuresis was copious. The amount of plasma proteins, the degree of renal concentrating power and the urinary changes progressed more slowly to normal. Though the red blood cell count and the hemoglobin value were nearly normal by the fourth week in August, leukopenia was still present. A slight decrease in the size of the heart and an increase in the amplitude of the waves were present in the teleoroentgenograms and electrocardiograms, respectively.

Operation.—On August 27, supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed by Dr. F. L. Adair under a combination of local infiltration and ethylene anesthesia. Somewhat more than the usual technical difficulties were experienced. The postoperative course was smooth. The patient was discharged on September 10 as much improved. At this time, she could have readily been ambulant, but she was kept to a rather vigorous regimen of rest.

Course.—In four subsequent returns for further study, on Nov. 10, 1930, and on Jan. 9, Feb. 27 and Sept. 25, 1931, the patient reported progressive improvement. She was able to do light housework. The white blood cell count was normal on the last two visits. All teeth had been extracted and plates substituted. The right border of the heart had receded to the right edge of the sternum, and the left was usually about from 9 to 9.5 cm. from the midsternal line in the fifth interspace. In the last visit, the left border of the heart was 8.5 cm. from the midsternal line. Rough systolic murmurs were heard over the apical and aortic regions, but they were less loud than before. They have been present throughout the period of observation.

The series of teleoroentgenograms presented a heart of increasingly normal configuration and decreasing size, but never entirely normal. The electrocardiograms displayed progressive increase in the amplitude of the waves.

In the final return, the patient mentioned that she had begun to notice a tendency to consciousness of increased heart rate, occurring with exertion and spontaneously. The condition is being further investigated.

Pathologic Report.—The uterus removed at operation measured 11 by 15 by 17 cm. It was symmetrically enlarged, nearly globular and contained an egg-shaped sac of a thick-walled and pedunculated submucous fibromyoma, measuring approximately 10 cm. in various diameters. The contents of the sac consisted of necrotic and hemorrhagic material.

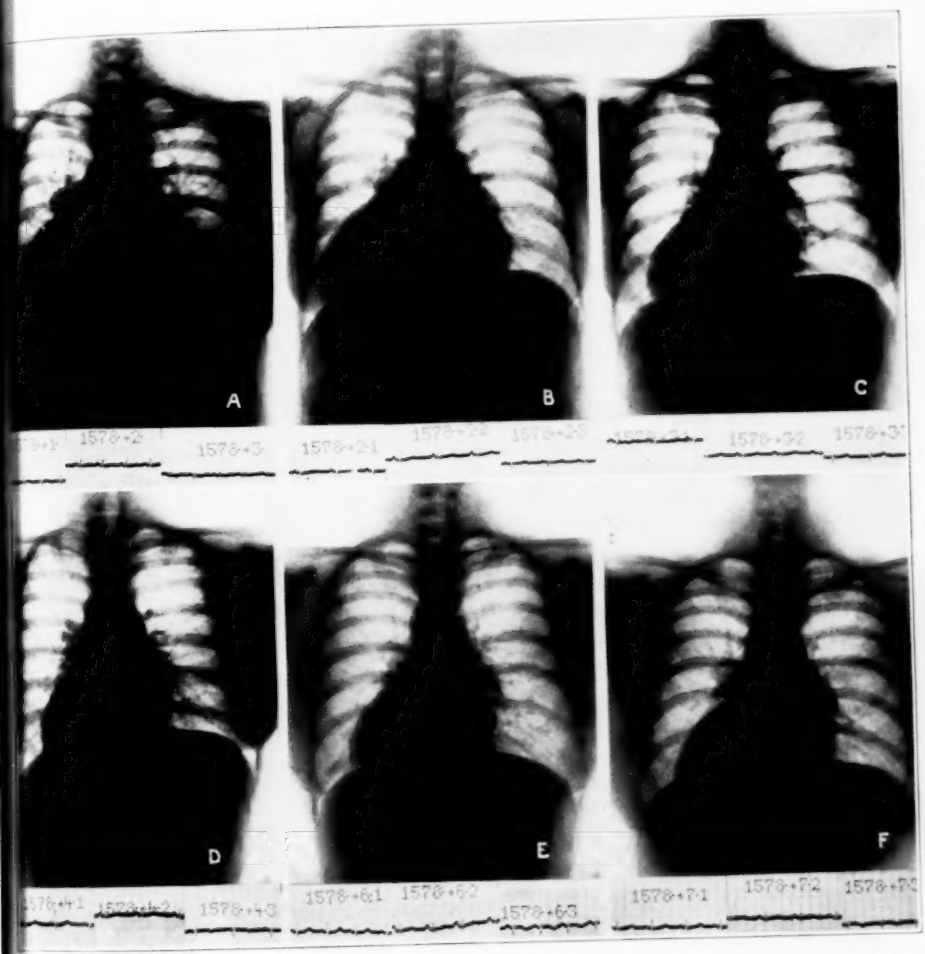


Fig. 3.—Showing electrocardiographic and teleoroentgenographic alterations. *A*, taken Aug. 11, 1930. (Mitral disease?). The heart is 65 per cent oversize; there is pulmonary congestion. Electrocardiographic curves are of low amplitude. *B*, taken August 25, shows condition unchanged from first picture. There is a tendency toward left axis deviation; the waves were slightly more increased in amplitude. *C*, taken September 8, shows heart now decreased to 40 per cent oversize. Waves are of slightly greater amplitude; left axis deviation remains. *D*, taken November 10, shows heart 25 per cent oversize. *E*, taken Feb. 26, 1931, shows size of heart 24 per cent over normal. *F*, taken Sept. 25, 1931, shows heart 31.4 per cent oversize. The electrocardiogram is unchanged in the last three pictures.

Microscopically, there were edema, hyalinization and shrinking of the muscle fibers and considerable deposition of dense collagenic connective tissue in the substance of the fibromyoma.

COMMENT

The rapid amelioration of the symptoms and signs during the course of rapidly repeated transfusions and the subsequent restoration of the condition of the blood to nearly normal, argues strongly, if only presumptively, that the anemia alone was responsible for the heart failure. The clinical picture, so far as the heart is concerned, can be explained on the basis of two types of activity imposed by the anemia. The first and early one involves the necessity of the use of the reserve function. According to Blumgart, Gargill and Gilligan,[34] from a study of the cardiac output in patients with anemia, there are an increased unsaturation of the hemoglobin, of minor importance, and an increase of cardiac output. The observation of increased cardiac output in the presence of experimentally produced hemorrhage in dogs has been noticed by Blalock and Harrison.[35] Along with the increased output of the heart there is a dilatation of the muscular wall. This is in no sense an indication of diseased muscle, but one of the manifestations of the process of compensation. The enlarged heart of this type returns rapidly to normal when the anemia disappears. The second type of activity represents the exhaustion of the reserve function and genuine damage to the myocardium, so that real heart failure supervenes. Anatomically, the heart muscle has been shown to present fatty changes and cloudy swelling. All of these changes have been well discussed by Walthard.[23]

In a search through the literature, there seems to be no mention of other cases as thoroughly investigated as the one of Ball.[36] The clinical, hematologic, teleoroentgenographic and electrocardiographic features were very much like those in the case that I have reported. A difference to be noted was that, though Ball's patient was first thought to have organic mitral stenosis, she presented a normal heart at the end of eleven months' of observation; in the patient discussed in this paper, probable mitral and possible aortic valvular lesions persisted, as residues, after the disappearance of the symptoms and signs. Ball gave a com-

34. Blumgart, H. S.; Gargill, S. L., and Gilligan, D. R.: Velocity of Blood Flow and Other Aspects of Circulation in Patients with "Primary" and Secondary Anemia, J. Clin. Investigation **9**:679 (Feb.) 1930.

35. Blalock, A., and Harrison, T. R.: The Regulation of Circulation: V. The Effect of Anemia and Hemorrhage upon the Cardiac Output of Dogs, Am. J. Physiol. **80**:157 (March) 1917.

36. Ball, D.: Changes in Size of the Heart in Severe Anemia, Am. Heart J. **6**:517 (April) 1931.

prehensive review of the literature dealing with clinical and other observations of the size of the heart in the presence of anemia.

From the teleoroentgenograms, it will be observed that early changes were much greater that later ones. The early ones are attributable to the rapid decrease of the anemia, the later possibly to the regimen of rest. It was thought that the shape of the heart in either of the first two photographs might be due to a pericardial effusion, which disappeared, like the fluid elsewhere in the body, during the period of recovery of the heart.

The increase in the amplitude of the waves in the electrocardiograms was interpreted as due to improved oxygenation of the myocardium.

The edema has a complex origin. It is directly referable to the failing heart, to the impoverished kidneys in the presence of the defective circulation and to the deficiency of the plasma proteins secondary to the loss of blood plasma. Through clinical and animal experimental investigation it has been demonstrated by Leiter,[37] Barker and Kirk,[38] Bruckmann and Peters,[39] Frisch, Mendel and Peters [40] and Bennett, Dodds and Robertson [41] that edema may occur exclusively in the presence of diminished plasma proteins. The rapid loss of edema and body weight (as indicated by fig. 2) may be due predominantly to replacement of the plasma protein as a result of the transfusions.

Since the heart had preexistent anatomic lesions, it was all the more sensitive to the effects of diminished hemoglobin and protein contents of the blood.

Other factors that may have influenced the illness of the patient were the severe infections about the teeth and the extensive suppuration of the tumor.

CONCLUSIONS

1. The case of a patient with severe anemia, heart failure, edema and fibromyoma of the uterus is reported, together with graphic representations of the changes in the hematologic and chemical conditions of the blood and teleoroentgenograms and electrocardiograms.

37. Leiter, L.: Experimental Edema, Proc. Soc. Exper. Biol. & Med. **26**:173 (Oct.) 1928; Experimental Nephrotic Edema, Arch. Int. Med. **48**:1 (Aug.) 1931.

38. Barker, M. H., and Kirk, E. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, Arch. Int. Med. **45**:219 (March) 1930.

39. Bruckmann, F. S., and Peters, J. P.: The Plasma Proteins in Relation to Blood Hydration, J. Clin. Investigation **8**:591 (June) 1930.

40. Frisch, R. A.; Mendel, L. B., and Peters, J. P.: The Production of Edema and Serum Protein Deficiency in White Rats by Low Protein Diets, J. Biol. Chem. **84**:167 (Oct.) 1929.

41. Bennett, T. I.; Dodds, E. C., and Robertson, J. D.: Plasma Protein Loss with Edema but Without Proteinuria, Lancet **2**:1006 (Nov. 8) 1930.

2. It is shown that the heart failure disappeared rapidly and nearly completely as the result of the abolition of the anemia by transfusions and operation.

3. The anemia, through its injurious effects on the heart muscle, causes compensatory changes in the heart, namely, an increased output per minute and dilation of the cavities, and later, as the cardiac reserve is exceeded, complete myocardial insufficiency.

4. The importance of the deficiency in plasma proteins in relation to the causation of edema is indicated.

5. Various views of the nature and cause of heart disease found in association with fibromyoma of the uterus are briefly discussed.

6. There exists no proof that fibromyoma of the uterus can directly injure the heart.

Dr. L. Leiter, Dr. F. L. Adair and Dr. J. C. P. Fearrington assisted in the preparation of this paper.

HYPERPARATHYROIDISM WITHOUT PARATHYROID TUMOR

REPORT OF A CASE IMPROVED BY PARTIAL PARATHYROIDECTOMY

LEWIS H. HITZROT, M.D.
AND
BERNARD I. COMROE, M.D.
PHILADELPHIA

The patient whose clinical record follows presented certain features that have recently been grouped together in the syndrome of hyperparathyroidism. She came under observation bedridden because of pain in the bones and muscular weakness. Examination disclosed extensive decalcification of the skeleton and an abnormally high blood calcium with excessive daily calcium output. Parathyroid tumor was searched for and none found. Removal of one apparently normal parathyroid gland produced no change in the symptoms or laboratory findings. When the surgeon, however, subsequently excised two similar anatomically normal glands on the opposite side, symptomatic improvement and a remarkable recalcification of the skeleton followed. The patient developed tetany postoperatively, which, however, gradually became more and more easily controlled, so that, twenty-two weeks after entry, she could be discharged competent to reenter her household routine. It is to emphasize the clinical significance of hyperparathyroidism without tumor that this case is being reported.

A brief résumé of the evolution of present knowledge of hyperparathyroidism is necessary in introducing this record. The relationship between the parathyroid glands, calcium metabolism and pathologic conditions of bone has been proved within the last six years. Previous to 1925, the physiology of parathyroid tissue being obscure, medical science approached the syndrome now recognized as hyperparathyroidism by describing merely its end-results. A pathologic entity known as generalized osteitis fibrosa cystica had been observed from time to time for thirty years after von Recklinghausen [1] had originally described it.

Read before the Section on Medicine of the College of Physicians of Philadelphia, Oct. 26, 1931.

From the Medical Clinic of the Hospital, and the Metabolic Section of the William Pepper Laboratory of Clinical Medicine, of the University of Pennsylvania.

1. von Recklinghausen, F.: Ueber Ostitis, Osteomalacie und Osteoplastiche Carcinose, Festchrift. Rudolph Virchow, zu seinem 71 Geburtstage, Berlin, G. Reimer, 1891.

Mention of coincident parathyroid tumor was made occasionally in the pathologic reports of osteitis fibrosa, but its significance was not suspected. Experimental study of the glands was devoted almost exclusively to the effects of extirpation. The complex calcium and phosphorus metabolism through which the parathyroid dyscrasia influenced the skeleton was unknown.

In 1925 the results of three important attacks on the problem began to appear. Collip [2] announced the discovery of the parathyroid homone and the preparation of a potent extract. This made experimental study of parathyroid activity possible. Mandl [3] of Vienna proved the etiologic relationship of the glands to osteitis fibrosa cystica. He implanted parathyroid tissue in a patient who had osteitis, made him worse thereby, then removed the implant plus a parathyroid adenoma and cured his patient. Finally, Aub and his co-workers [4] were prosecuting a series of studies in mineral metabolism which have established the links by which the glands and the skeletal changes are related.

Clinical hyperparathyroidism, in the light of present knowledge, may tentatively be divided into two types, the primary, with benign or, rarely, malignant tumor of the parathyroid gland, and the secondary, with functional hyperactivity and at times glandular hyperplasia. In the former case, the high serum calcium, negative calcium balance and decalcification of bone result as the number of active parathyroid cells increases. In the latter type, the etiology is not entirely clear. Hyperactivity is thought, however, to follow a prolonged low intake of calcium, in which the glands, to keep blood values normal, progressively remove calcium from the storehouses in the bones. The depletion of the bones may go on, as a result of this overcompensation, long after the actual need for the stored calcium has passed. When the parathyroid glands have failed to revert to normal activity and cortical as well as spongy bone has become greatly decalcified, symptoms appear.

The majority of reported cases of hyperparathyroidism have been well advanced when they reached competent medical hands. Nevertheless, wide variations in the roentgenologic picture of bone have been found, dependent chiefly on the two factors of duration and degree of glandular hyperactivity. It is thus clear that one must now consider

2. Collip, J. B.: Extraction of a Parathyroid Hormone Which Will Prevent or Control Parathyroid Tetany and Which Regulates the Level of Blood Calcium, J. Biol. Chem. **63**:395, 1925.

3. Mandl, F.: Therapeutischer Versuch bei einem Falle von Ostitis fibrosa generalisata mittels Extirpation eines Epithelkörperchentumors, Zentralbl. f. Chir. **53**:260, 1926.

4. Albright, F.; Bauer, W.; Ropes, M., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism, J. Clin. Investigation **7**:139, 1929.

osteitis fibrosa cystica generalisata as one manifestation of the late stage of an endocrine-metabolic disease.

The treatment of the primary form of hyperparathyroidism is surgical removal of the tumor. In the six years that have followed Mandl's pioneer operation, successful results following excision of the tumor have been reported in sufficient number to establish the operation firmly.

On the other hand, reports of therapeutic removal of parathyroid tissue when no tumor is found are scarce. Richardson,[5] operating on the patient with osteitis studied by DuBois and co-workers[6] and Bauer et al.,[7] made adequate search of the parathyroid bed. He found no tumor, and thereupon removed two normal-appearing glands. There resulted some symptomatic but no metabolic benefit in what was a far advanced case. Dresser and Hampton[8] recently reported the therapeutic removal of two normal parathyroid glands without benefit to the patient. One cannot be certain from the report, however, that the whole parathyroid region was examined at operation for possible tumor. It is possible, furthermore, that in both these instances excision of a third gland would have brought the desired result. Leriche,[9] of Strasbourg, finding hypercalcemia in certain cases of ankylosing polyarthritis, removed in each case an apparently normal parathyroid gland with symptomatic benefit to the patient.

Only Ballin and Morse,[10] very recently, have removed normal glands in hyperparathyroidism with clinical success. As in the case presented here, hyperplasia could not be detected by ordinary histologic examination.

REPORT OF CASE

History.—E. L., an Italian widow of 42 years, entered the medical clinic of the Hospital of the University of Pennsylvania on Feb. 2, 1931, complaining of weakness and aching pain in the bones. The patient had been obese since childhood, but up to the present illness of the past four years had always considered herself

5. Richardson, E. P.: Aub, J. C., and Bauer, W.: Parathyroidectomy in Osteomalacia, Ann. Surg. **90**:730, 1929.

6. Harmon, E. E.; Shorr, E.; McClellan, W. S., and DuBois, E. F.: A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies, J. Clin. Investigation **8**:215, 1930.

7. Bauer, W.; Albright, F., and Aub, J. C.: A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies; Metabolic Study II, J. Clin. Investigation **8**:229, 1930.

8. Dresser, R., and Hampton, A. O.: Osteitis Fibrosa Cystica Generalisata with Hyperparathyroidism as Etiology, Am. J. Roentgenol. **25**:739, 1931.

9. Leriche, R., and Jung, A.: Position actuelle du problème de la polyarthrite ankylosante et de son traitement par les opérations parathyroidiennes, Lyon chir. **28**:408, 1931.

10. Ballin, M., and Morse, P. F.: Parathyroidism, Am. J. Surg. **12**:403, 1931; Parathyroidism and Parathyroidectomy, Ann. Surg. **94**:592, 1931.

healthy. There was evidence that her diet for many years had been deficient in respect to calcium-containing foods and the fat-soluble vitamins, in that she had shunned milk, butter, cream and cheese, and had eaten little fish, meat, eggs or fruit. Her diet had consisted mainly of starches and vegetables. Five of six pregnancies had ended in miscarriage (induced?). The second pregnancy went to term. The last miscarriage had occurred six years before entry, two years before the onset of the pain in the bones. No other factor in the past history suggested syphilis, and the Wassermann reactions of the blood at various times recently had all been negative.

At the onset of her illness, the patient was living the usual life of a housewife in marginal circumstances in a small New Jersey town. Her husband and one child were well. There was no mental or physical strain. The onset was evi-

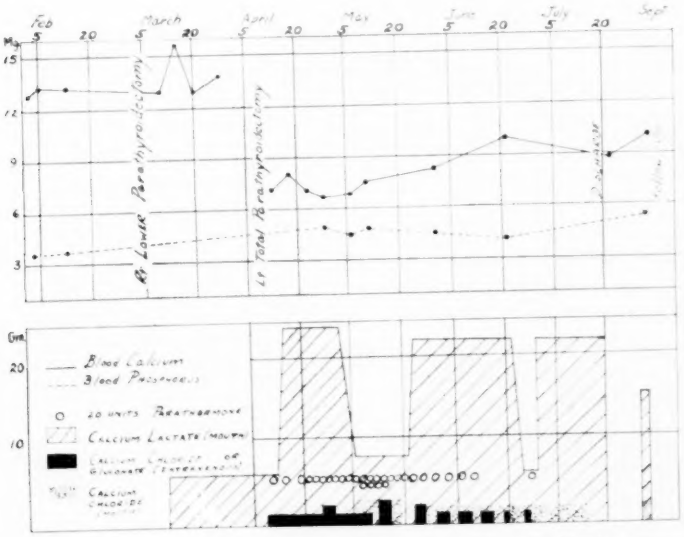


Fig. 1.—Chart showing the blood chemistry in correlation with the treatment in a case of hyperparathyroidism.

dently gradual. A dull, boring ache began in the legs and progressed until the patient hobbled about bearing as much weight as possible on her hands by taking hold of chairs, tables, etc., as she walked. Several weeks before entry she became bedridden. During the latter period, motion produced considerable pain, poorly localized, in any of the bones moved. There was also increasing weakness.

The discomfort had led the patient, one year previous to the clinic's acquaintance with her, to another hospital, where roentgenographic study of several bones was made. The films, in the light of the present knowledge of the case, show definite generalized osteoporosis; at the time, they were considered to be imperfect films, and no diagnosis was made. In November, 1930, ten weeks before entry, a second set of films showed, in addition, irregular areas of extreme decalcification, which led Dr. Howard Curtis of Moorestown, N. J., the patient's physician, to refer her to the University Hospital for study.

Physical Examination.—Examination on entry showed a short, obese Italian woman in considerable discomfort on motion even while in bed. Her family and friends readily agreed that she had grown shorter during her illness (as evidenced by the flattening of the vertebrae shown in the roentgenographic films). There was no kyphosis, however, no abnormal bowing of the long bones and no evidence of fracture. The muscles in general were hypotonic. There was moderate tenderness to pressure over the long bones. The teeth were in good condition.

No abnormality could be made out in the region of the thyroid gland, which was barely palpable. The electrical reactions of the muscles reached the highest

Fig. 2.—Roentgenographic appearance of the pelvis on admission. Note the transparency of the bone, the areas of extreme decalcification in the ilia and the narrowing of the bodies of the vertebrae.

normal limit, but they were not pathologically prolonged. Otherwise the physical examination showed normal conditions.

Laboratory Findings.—The results of routine examination of the blood and urine were normal. The result of the test for Bence-Jones protein in the urine was negative. The basal metabolic rate was + 11, which is within normal limits. The figures for blood serum calcium and inorganic phosphorus, on the other hand, are noteworthy. The serum calcium, by the modified Tisdall method,[11] was dis-

11. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium, with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

Fig. 3.—Biopsy of the tibia; Mallory connective tissue stain; × 18. The loss of substance of the cortex, with widened marrow extensions, gives a spongy rather than compact appearance to the bone. Compare the normal cortex shown in figure 4.

Fig. 4.—Normal cortex of tibia; Mallory connective tissue stain; × 18.

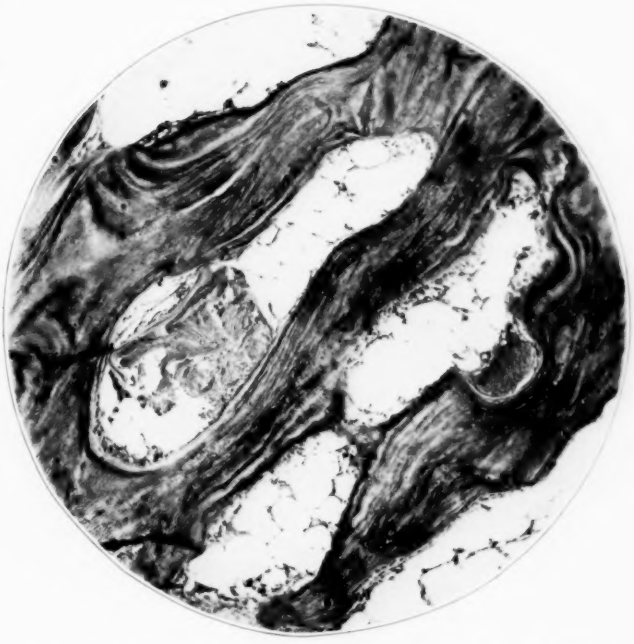


Fig. 5.—Biopsy of tibia; iron-hematoxylin stain; × 59. Porous bone, with encroaching fatty marrow. There is an increased amount of osteoid tissue, devoid of calcium; practically no cellular activity, either of osteoblasts or osteoclasts, is seen. A few small foci of fibrosis in the marrow are found in study of the sections. Occasional large wandering cells are to be found. Compare the normal cortex shown in figure 6.

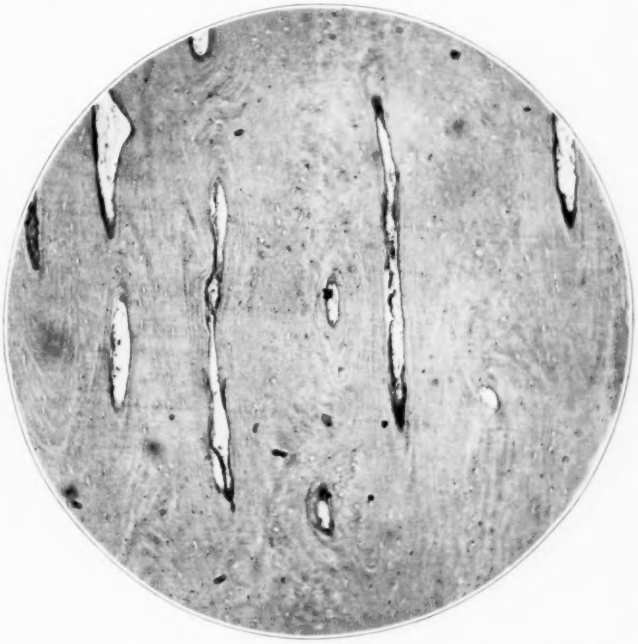


Fig. 6.—Normal cortex of tibia; hematoxylin-eosin stain; × 59.

tinctly elevated to 12.7 and 13.2 mg. per hundred cubic centimeters on two separate days. The blood phosphorus, determined by the method of Fiske and Subbarow,[12] was moderately lowered to 3.3 mg. per hundred cubic centimeters.

The patient did not cooperate well in eating calcium-containing foods, but on a measured intake approximating 0.5 Gm. of calcium daily, the urinary calcium in twenty-four hours amounted to 0.410 Gm., a figure above normal for that intake and indicating a negative balance. The figures for serum protein fell within the normal range. Variations in the significant laboratory data are indicated in figure 1.

Roentgenologic Report.—The films of the patient's skeleton were examined by Dr. H. K. Pancoast and members of his staff with considerable interest. They were not typical of the usual roentgenograms of bone changes in generalized osteitis fibrosa cystica, probably because they were not of the advanced stage. They did show, however, rarefaction of all bones and narrowing of the vertebral bodies. There were multiple areas of localized extreme rarefaction in the pelvis, right femur and right humerus (fig. 2). Films of the urinary tract were negative for calculi.

Clinical Course.—Surgical treatment was not instituted at once. Instead, the effects of a diet high in calcium and high in phosphorus (0.765 and 3.50 Gm. daily, respectively), cod liver oil and heliotherapy were tried for one month. There was not the slightest improvement in symptoms or in laboratory findings. The patient was then transferred to the service of Dr. Charles H. Frazier, who explored the region of the right parathyroid glands, found nothing abnormal, and removed the parathyroid body at the lower pole. The gland was of normal size and histologic structure. The operation failed to alter the symptoms or the figures for calcium, and at the end of another month the roentgenologic picture of the bones was unchanged.

Five weeks after the first operation, the second parathyroidectomy was done. Dr. Henry F. Ulrich, assistant to Dr. Frazier, removed the left lobe of the thyroid gland in order to make certain of securing the parathyroid glands, which, two in number, were, like the first, of normal size and histologic structure.

On the third postoperative day tetany developed, as is not unusual in such procedures. The serum calcium, which had been 13.8 mg. per hundred cubic centimeters just before operation, was determined during the first day of tetany to be 6.8 mg. per hundred cubic centimeters, a tetanic level. The regimen instituted to control the tetany included large daily doses of calcium lactate (from 10 to 20 Gm.), calcium chloride in 1 Gm. doses given intravenously, as the attack developed, supplemented by calcium gluconate in doses of from 10 to 30 cc. given intravenously or intramuscularly, and Collip's parathyroid extract (Parathormone-Lilly) in 20 unit doses, intramuscularly, about every second day. The diet high in calcium and high in phosphorus was continued, and the patient was given viosterol daily (fig. 1).

The roentgenograms of the bones three weeks after operation remained unchanged. A biopsy of the cortex of the right tibia was made in a region showing, roentgenographically, irregular areas of decalcification. Microscopic sections of this bone confirmed the diagnosis of osteoporosis, in a stage, probably, before generalized fibrosis had taken the place of the calcium-free bone matrix (figs. 3 and 5).

12. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

The patient began to improve symptomatically from this point. She gradually needed less and less intravenous and intramuscular calcium and parathyroid extract to control the tetany. Two months after operation she was practically free from pain in the bones, felt stronger, and gradually began to move about, first in a chair and then on her feet.

More significant than all other indications of betterment, however, were the roentgenographic films, which, nine weeks after operation, showed a definite increase in deposit of lime throughout; the architecture of the bones was more distinct (fig. 7). The figures for blood calcium and phosphorus were now within normal limits, 9.8 and 4 mg. per hundred cubic centimeters, respectively. Incidentally, the basal metabolic rate did not fall as a result of the extirpation of one lobe of the thyroid gland.

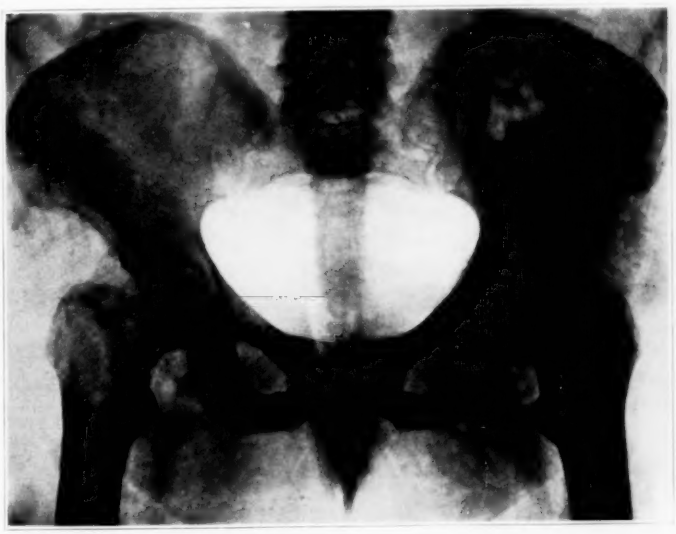


Fig. 7.—Appearance of pelvic bones on June 16, nine weeks after parathyroidectomy. The shadow is generally darker; the irregular rarefied areas have disappeared.

Calcium medication now consisted of the lactate, an average of 20 Gm. daily by mouth, 2 Gm. of the chloride by mouth, and parathormone in 20 unit doses twice weekly.

The patient was discharged to her home on July 14, 1931, five and one-half months after entry, walking about without discomfort except for moderate lumbar pain, probably due to functional strain. She paid a follow-up visit to the ward in September, five months after operation. Further calcification of the skeleton was reported, the blood calcium and phosphorus were within normal limits, and the patient's calcium balance was positive. She remained free from tetany on a daily regimen of 15 Gm. of calcium lactate and 2 Gm. of the chloride by mouth.

COMMENT

Certain points of the record merit emphasis as illustrating the variability in the picture of hyperparathyroidism.

It is not known why this woman, whose childhood and youth were evidently normal, and whose adult life varied little from the ordinary, should develop at 40 an extensive osteoporosis. The recognized causes of osteoporosis were not operative, except perhaps a long-standing, mild dietary deficiency in foods high in calcium and vitamins A and D. One may speculate that the deficiency may have led to gradual overfunction of the parathyroid glands as they undertook to supply the body's calcium needs from the reservoirs in the bones. Marine [13] and Luce [14] demonstrated that a diet low in calcium will cause hyperplasia of the parathyroid glands in animals.

The three parathyroid glands that were removed showed no variation from the normal, by present criteria of judgment. In this connection one must keep in mind, however, that the size of the parathyroid gland varies considerably, and, as all observers agree, minor grades of hyperplasia may exist without being demonstrable by ordinary methods. It is not uncommon, moreover, in similar organs, for functional dyscrasia to exist without recognizable anatomic change; this may well occur in the parathyroid gland.

Decalcification here, as in other reported cases, was evidently slow. The symptoms, however, were more distressing than those usually found. That fact led to earlier hospitalization and treatment before decalcification had reached the stage of deformities and fractures.

The facts that removal of one parathyroid body had no effect on the symptoms and that all three glands were similar in size and structure suggest that all were equally involved. It was known that at least one parathyroid gland remained in situ after operation, and that in accordance with clinical and experimental evidence,[15] if tetany ensued, the remaining tissue would in time develop at least partial compensatory power. From the favorable course of the symptoms of tetany there is every reason to suspect that this occurred in the present instance.

The thought may arise that excision of a portion of the thyroid gland, rather than the parathyroidectomy, may have been responsible for the favorable result, for osteoporosis has been observed in certain

13. Marine, D.: Parathyroid Hypertrophy and Hyperplasia in Fowls, Proc. Soc. Exper. Biol. & Med. **11**:117, 1913.

14. Luce, E. M.: The Size of the Parathyroids of Rats and the Effect of a Diet Deficiency of Calcium, J. Path. & Bact. **26**:200, 1923.

15. Tanberg, A.: The Relation Between the Thyroid and Parathyroid Glands, J. Exper. Med. **24**:547, 1916. Guy, C. E.: Adenoma of the Parathyroid, Arch. Path. **3**:352 (Feb.) 1927.

cases of hyperthyroidism by Aub and his co-workers [16] and others. All the available evidence, however, indicates that changes in the bones occur only in long-standing hyperthyroidism, which this patient certainly did not have. Furthermore, hyperthyroidism increases calcium output, but does not alter the calcium content of the blood. The serum calcium here was consistently high, and subsequent restoration of bone was demonstrably associated with the lowering of that figure.

SUMMARY

The foregoing clinical record represents a moderately advanced state of hyperparathyroidism in which medical measures failed to bring relief. Pain in the bones and extensive decalcification were prominent symptoms and led to hospitalization before the advanced skeletal disease, with fibrosis and cystic degeneration, had developed. There was no parathyroid tumor.

Surgical excision of one parathyroid body was of no apparent benefit. Subsequent removal of two of the remaining parathyroid bodies brought about a dramatic fall of the blood calcium, with tetany. As the severity of the tetany subsided there developed a remarkable recalcification of the diseased bone, progressing in five months to an essentially normal roentgenographic picture of the skeleton.

The result that followed removal of the three parathyroid glands left no doubt that in them lay the cause of the patient's illness. Hyperplasia was not demonstrable.

The course of this patient's illness indicates that, when clinical findings signify overactive parathyroid glands, surgical removal of considerable parathyroid gland tissue is justified, even though the operator sees no gross evidence of abnormality therein.

16. Aub, J. C.; Bauer, W.; Heath, C., and Ropes, M.: Studies of Calcium and Phosphorus Metabolism: III. The Effects of the Thyroid Hormone and Thyroid Disease, J. Clin. Investigation **7**:97, 1929.

RELATIONS BETWEEN PRIMARY HYPOCHROMIC ANEMIA AND CHLOROSIS

ARTHUR L. BLOOMFIELD, M.D.
SAN FRANCISCO

Under the designation of hypochromic anemia [1] (primary, microcytic, idiopathic, achylic) there have appeared in the recent literature [2] a number of reports. They concern themselves with a disorder featured by an anemia with a low color index and small erythrocytes, and usually by gastric anacidity, which occurs almost exclusively in women in from the third to the fifth decade. The implication of most of the current writings is to the effect that this syndrome is a specific disease; some authors (Witts,[3] Dameshek,[4] Mills [5] and Vanderhoof and Davis [6]) have definitely stated that such is their belief. Furthermore, although this is admitted to be a chlorotic type of anemia, it is usually claimed that it is not chlorosis but rather an entirely distinct entity. That chlorosis, so common in the practice of physicians a generation ago, should have vanished and that a new type of chlorotic anemia should have appeared is a question of sufficient interest to justify critical discussion, and my present purpose is not primarily to add further case reports to the literature of "hypochromic anemia," already well documented, but to analyze the evidence bearing on its claims to definite identity as well as on its relation to the disease chlorosis.

IS THE "HYPOCHROMIC ANEMIA" OF CURRENT WRITERS A DEFINITE DISEASE?

Most of the recent reports trace the genesis of hypochromic anemia as a distinct entity to the work of Faber and of Faber and Gram,[7] who emphasized the frequent occurrence of anemia with a low color index

From the Department of Medicine, Stanford University School of Medicine.

1. Henceforth in this paper, for the sake of convenience, the condition will be referred to as "hypochromic anemia."

2. Waugh, T. R.: Hypochromic Anemia with Achlorhydria, Arch. Int. Med. **47**:71 (Jan.) 1931.

3. Witts, L. J.: Simple Achlorhydric Anemia, Guy's Hosp. Rep. **10**:253, 1930.

4. Dameshek, W.: Primary Hypochromic Anemia, Am. J. M. Sc. **182**:520, 1931.

5. Mills, E. S.: Idiopathic Hypochromemia, Am. J. M. Sc. **182**:554, 1931.

6. Vanderhoof, D., and Davis, D.: Anemia of the Microcytic Type in Middle-Aged Women, Tr. A. Am. Physicians **46**:284, 1931.

7. Faber, K., and Gram, H. C.: Relations Between Gastric Achylia and Simple and Pernicious Anemia, Arch. Int. Med. **34**:658 (Nov.) 1924.

in patients with gastric anacidity. There was nothing in Faber and Gram's paper, however, to indicate that they regarded this anemia as anything more than a "complication" of achylia; they pointed out that it was of a benign character, although it tended to recur, and that the response to an iron preparation was satisfactory. Without reviewing in detail the numerous subsequent studies that have culminated in the recent concept of hypochromic anemia as a distinct disease, the features of the condition about which all writers agree may now be summarized:

1. The disorder occurs almost exclusively in women.

2. It is essentially a disease of middle life (from 30 to 50 years).

3. It is a mild chronic or relapsing disorder which does not directly lead to a fatal outcome.

4. Symptoms, if present, are those of general lack of well-being and such non-specific disturbances as come with any anemia. The patients are usually not "physically fit."

5. The pallor is "white," and there is no icterus as in addisonian anemia.

6. Gastric anacidity is characteristic.

7. The blood shows an anemia with small cells and a relatively marked decrease in hemoglobin, and color indexes of 0.6 or lower are the rule.

8. Megaloblasts are not present.

9. There is no hyperbilirubinemia.

10. The bone marrow is hyperplastic and is crowded with normal erythroblasts and normoblasts (Dameshek).

11. There is no demonstrable external cause, such as bleeding from abnormal sources.

12. There is no improvement after the ingestion of liver, but the administration of iron or of iron and copper preparations is followed by a rapid increase in the hemoglobin and cell count.

But no sooner has one laid down these criteria than exceptions and variations begin to appear in great numbers. The condition is not confined to women. Dameshek,[4] for example, among his seven cases reported an instance in a man of 29 years who, without demonstrable cause, had a severe anemia of the type under discussion. The hemoglobin was 42 per cent, the erythrocytes were 3,470,000, and the average red blood cell diameter was 6.14 microns. There was a prompt response to an iron preparation after liver had failed. The only atypical feature was the presence of free hydrochloric acid in the gastric secretion. Witts [2] also reported a case in a man, and I studied a young Japanese who had the trouble in typical form, including gastric anacidity after histamine. The disorder is not confined to middle age but may occur in young people. In Dameshek's case 3 a woman aged 23 years "had been more or less pale since infancy and had never been strong." In Mills' [5] case 8 the patient was 26 years old and had been anemic for ten years. In his case 1 the patient, although 40 years of age at the

time of the study, said she had "always" been anemic. In McCann's [8] case 1 the patient complained of "perpetual fatigue and pallor." "These symptoms dated from early childhood." McCann's case 3 was that of a young woman of 19 years. "For five years she was notably pale." There are also some aberrations in the physical findings. A number of patients are reported to have had papillary atrophy of the tongue, and this has been so twice in our own experience. In other reports (McCann and Dye [8]) splenomegaly has been stressed as a feature. All sorts of complicating disorders, infections and disabilities are described in various cases. Gastric anacidity is not constant, and even without the crucial histamine test a number of cases have been described in which free hydrochloric acid was present (Mills,[5] Dameshek [4] and Vanderhoof and Davis [6]). I have also studied a condition otherwise indistinguishable from the disorder under discussion except for the presence of normal gastric acidity. The statement commonly made that there has been no loss of blood must always be open to question when women are concerned. Such notes as "she developed increased menstrual flow, and at times would flow between periods" (Dameshek,[4] case 1) are not uncommon, and even though the patient regards the flow as normal, she often has no valid standard of comparison.

A consideration of the preceding analysis would seem to make it clear that the "characteristic" features of hypochromic anemia are subject to so many exceptions that the greatest caution must be used in setting up this disorder as a specific disease. In support of this point of view I wish to quote my experience which includes, in addition to cases of the "typical hypochromic anemia" of current writers, patients who illustrate the following variations:

1. Patients with unexplained gastric anacidity in perfect health and with normal blood.

2. Patients with unexplained gastric anacidity with all degrees of anemia (hypochromic), showing a gradation from a normal count to outspoken deficiency.

3. Patients with severe anemia of the type under consideration but with slight degrees of gastric acidity.

4. Patients with severe anemia of the type under consideration but with normal gastric acidity.

The following cases illustrate these various types.

CASE 1.—*Unexplained gastric anacidity in a woman of 26 years without anemia.*

Mrs. N. D. (case 199503), aged 26, a housewife, entered the clinic because of a variety of minor complaints. The family and past histories were not remarkable, although at times she had vague indigestion with gas. There was no special

8. McCann, W. S., and Dye, J.: Chlorotic Anemia with Achlorhydria, Splenomegaly and Small Corpuscular Diameters, Ann. Int. Med. **4**:918, 1931.

menstrual abnormality. On examination she looked well and weighed 120 pounds (54.4 Kg.). There were no abnormal physical findings. The stools were normal, as were gastro-intestinal roentgenograms, but gastric analysis (histamine) yielded only small amounts of mucus with no free hydrochloric acid. Study of the blood showed: red blood cells, 5,000,000; hemoglobin, 15.48 Gm. or 90.3 per cent (Sahli); color index, 0.9; white blood cells, 14,250; polymorphonuclears, 77 per cent; eosinophils, 1 per cent; basophils, 2 per cent; lymphocytes, 15 per cent; monocytes, 5 per cent; platelets, 440,000; reticulocytes, 1.2 per cent; average red cell diameter, 7.65 microns; smear, normal.

Comment.—This case is presented to emphasize one end of the series in contrast to the next group which will illustrate, in patients with anacidity, the gradual transition from normal blood to the outspoken syndrome of hypochromic anemia.

Cases of Unexplained Anacidity with Various Degrees of Anemia

Case	Patient	Age	Sex	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Comment
199503	D.	26	F	5.00	90	0.9	Vague general complaints
A 9408	M.	47	F	4.7	85	0.9	Clinical diagnosis: psychoneurosis
197213	W.	65	F	4.28	74	0.87	Mild indigestion for years
A 16760	We.	54	F	4.33	69	0.8	Nervous breakdown
137042	T.	44	F	3.23	60	0.9	Chronic arthritis
A 10982	A.	36	F	3.41	43	0.63	Nervous breakdown: menstrual flow scanty; some recent hemorrhoidal bleeding
181922	V.	50	F	1.65	21	0.63	Excessive uterine bleeding for two years

GRADATIONS OF ANEMIA IN PATIENTS WITH GASTRIC ANACIDITY

Every grade of anemia may be associated with gastric anacidity, and to illustrate this point the following cases have been selected from the files (table). The anacidity in every instance was classified as "unexplained";[9] that is, it was an incidental finding in patients who had no evidence of either pernicious anemia or cancer of the stomach. Transitions from normal blood (patient D.) to outspoken anemia of the "hypochromic" type of which case A10982 is a typical instance are shown. It would serve no purpose to add to the literature more cases of typical hypochromic anemia, but the following instance in a young man seems worthy of record.

CASE 2.—*Severe hypochromic anemia in a man of 29 years without evidences of loss of blood.*

M. T. (case A 17347), a Japanese farm laborer, aged 29, entered the hospital with the complaint of weakness. The past history yielded no explanation for an anemic state; there had been no loss of blood, and the diet appeared adequate. For several years there had been increasing loss of weight and weakness. There were

9. Polland, W. S., and Bloomfield, A. L.: Unexplained Anacidity, Arch. Int. Med. **48**:412 (Sept.) 1931.

no digestive symptoms. Examination revealed a small, well muscled man who did not appear very ill. There was marked pallor without any suggestion of icterus. The tongue was normal, the spleen was not palpable and there were no proprioceptive changes in the extremities. There were signs of an old inactive apical tuberculosis.

The Wassermann reaction was negative and the icterus index 6; the histamine test for gastric secretion showed complete absence of free hydrochloride acid. Roentgenograms of the gastro-intestinal tract were normal. Examination of the blood showed: red blood cells, 4,640,000; hemoglobin, 51.7 per cent (8.8 Gm. per hundred cubic centimeters); color index, 0.56; cell volume, 29; volume index, 0.732; white blood cells, 9,370; polymorphonuclears, young forms, 12 per cent and segmented forms, 66 per cent; eosinophils, 2 per cent; lymphocytes, 15 per cent; monocytes, 5 per cent; platelets, 464,000; reticulocytes, 1.3 per cent. A smear showed marked anisocytosis and poikilocytosis, and polychromasia. No normoblasts or megaloblasts were seen. The red cells varied in size from 4.37 to 11.25 microns.

Course.—The patient improved rapidly on an iron preparation. Fourteen days after therapy was started, the blood showed: red blood cells, 5,000,000, and hemoglobin, 75 per cent. The patient felt perfectly well.

Comment.—Aside from age and sex this case is a typical instance of hypochromic anemia. It illustrates well the futility of the rigid criteria that have been arbitrarily laid down in the recent literature. Certainly the condition might with equal propriety be designated as "male chlorosis."

One may next turn to a different variant of the syndrome under discussion, namely, severe anemia of the hypochromic variety without gastric anacidity.

CASE 3.—*Typical hypochromic anemia syndrome in a middle-aged woman with subacidity but without anacidity.*

A woman (case A 4557), aged 45, entered the clinic with the complaint of weakness and palpitation. The past history was not remarkable except for the presence of hemorrhoids for years. There had been occasional slight bleeding from the rectum, but no excessive menstrual flow. For several months she had noted increasing weakness, fatigability and shortness of breath on exertion. She had fainted several times after standing for a long time. She said that there had recently been an increase of the hemorrhoidal bleeding. On examination, aside from pallor, nothing remarkable was made out. There were some internal hemorrhoids which did not bleed at the time of the proctoscopy.

The Wassermann reaction was negative, the icterus index 4.7, and after histamine stimulation the highest gastric acidity attained was only 30 (total acidity), the average normal by this procedure being about 100. Roentgenograms of the gastro-intestinal tract were normal. Examination of the blood showed: red blood cells, 3,790,000; hemoglobin, 6.9 Gm. per hundred cubic centimeters (40.5 per cent); color index, 0.53; white blood cells, 7,260; polymorphonuclears, 70 per cent; basophils, 1 per cent; lymphocytes, 24 per cent; monocytes, 5 per cent; platelets, 492,700; reticulocytes, 1.4 per cent. A smear revealed anisocytosis, poikilocytosis and polychromasia.

Comment.—The anemia in this case clearly seems to be due, in part at least, to bleeding from hemorrhoids. However, aside from the presence of a small amount of acid in the gastric secretions, the picture that resulted is typical of hypochromic anemia.

CASE 4.—*Typical hypochromic anemia syndrome in a woman with normal gastric secretion.*

Mrs. E. D. (case A 16698), a clerk, aged 38, entered the hospital with the complaint of weakness. The past history was unimportant except for the fact that hysterectomy was done two years before for excessive menstrual bleeding. She had had hemorrhoids to a slight degree for years, but had not noticed any special bleeding. About a year before examination she began to feel weak. Since then great lassitude, palpitation and dyspnea on exertion had developed. Examination showed nothing remarkable aside from pallor. Through the proctoscope one could see some internal hemorrhoids, which were not extensive; there was no bleeding at the time.

The Wassermann reaction was negative, the stool showed no occult blood, and the histamine test revealed practically normal gastric secretion (highest acidity, 83). Examination of the blood showed: red blood cells, 3,710,000; hemoglobin, 40 per cent; color index, 0.54; white blood cells, 6,600; polymorphonuclears, 53 per cent; eosinophils, 1 per cent; lymphocytes, 40 per cent; monocytes, 5 per cent. A smear revealed very pale red cells, with poikilocytosis and anisocytosis.

Course.—A hemorrhoidectomy was done, following which the patient was given large doses of iron and ammonium citrate with, later, the addition of 60 mg. of copper sulphate daily. In seventeen days the hemoglobin was 84 per cent and the red cell count 5,270,000 and the patient felt perfectly well.

Comment.—Bleeding from hemorrhoids may have played a part in precipitating the anemia in this case, although as far as could be determined the loss of blood was very slight. At any rate, aside from the normal gastric secretion, the picture was typical of hypochromic anemia and the characteristic response to iron and copper preparations was readily obtained.

In summary, the foregoing cases illustrate that variations of all sorts from typical hypochromic anemia are encountered, and that they blend insensibly with this typical picture. One may find cases of gastric anacidity with the condition of the blood varying from normal to extreme anemia; one may find cases of severe hypochromic anemia with anacidity, subacidity or normal acidity.

The preceding analysis and reports of cases seem to me incompatible with the concept of a specific disease, achylic hypochromic anemia. It must be admitted that the combination of anacidity and anemia not uncommonly occurs in middle-aged women, but the vast majority of achylic women are not markedly anemic nor do all anemic women by any means have achylia. It seems as if some special concatenation of circumstances is necessary to produce the full blown syndrome, but until much more is known about iron storage and metabolism, as well

as the conditions governing blood formation and destruction, it will serve no useful purpose to set up a definite disease on the basis of criteria to which so many and such obvious exceptions exist.

IS THE HYPOCHROMIC ANEMIA SYNDROME RELATED TO CHLOROSIS?

Most of the recent writers, with the exception of Adamson,[10] assert dogmatically that hypochromic anemia is entirely distinct from chlorosis. The principal arguments that have been advanced are (1) that the former occurs in middle-aged women, whereas the latter is confined to young girls, (2) that the "green" color of chlorosis is not seen in hypochromic anemia, (3) that chlorosis is never associated with as severe an anemia as is encountered in the "hypochromic" cases in adults and (4) that in chlorosis there is hyperacidity rather than anacidity. Some writers allege critical differences in symptomatology.

Many older clinicians (in conversation) cling in an almost sentimental manner to the idea that chlorosis is a highly specific disease, stressing always the characteristic (greenish) facies, the occurrence in undernourished young women with menstrual disorders, and the response to iron preparations. Naegeli [11] carried this to a naive extreme when, having arbitrarily laid down the dictum that chlorosis occurs only in women, he refused to accept identical cases in males because they were in the wrong sex. It seems in order, then, to turn to the actual descriptions and records in the literature in the attempt to clarify the subject.

Age.—In his masterly article on chlorosis Albutt [12] emphasized the fact that the onset is usually at or shortly after puberty. He believed, however, that the disease occurs in later life, in which case it "is to be regarded as a relapse." Osler [13] also mentioned the occurrence of attacks in women of middle age. Witts,[14] under the heading of "Late Chlorosis," described a series of cases in women over 30 years old identical with his cases of hypochromic anemia except that acid was present in the gastric secretions. It appears, then, that as regards age, chlorosis and hypochromic anemia merge insensibly into one another. In the former the patient may have "relapses" in later life; with the latter the patients often give a story of anemia since childhood.

---

10. Adamson, J. D.: Chronic Chlorosis, Canad. M. A. J. **24**:793, 1931.

11. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 5, Berlin, Julius Springer, 1931, p. 306.

12. Albutt, T. C., in Albutt and Rolleston: System of Medicine, London, 1909, vol. 5, p. 681.

13. Osler, W., in Pepper, W.: An American Text Book of the Theory and Practice of Medicine, Philadelphia, W. B. Saunders Company, 1894, vol. 2, p. 196.

14. Witts, L. J.: Late Chlorosis, Guy's Hosp. Rep. **11**:205, 1931.

Sex.—Occasional cases in boys and men indistinguishable from chlorosis are recognized by various writers (Albutt, Osler). The subject was recently discussed by Witts.[15] He reported five cases in young men under the heading of "male chlorosis." The findings and the response to iron preparations are identical with those described in connection with "typical hypochromic anemia." It is of particular interest that both with hypochromic anemia in adults and with chlorosis, males are affected in about the same small proportion of cases, a fact which, if it has any significance, would tend rather to relate than to differentiate the two conditions.

Symptoms.—It would serve no purpose to quote at length the actual descriptions of chlorosis as compared with hypochromic anemia. The reader can convince himself in a moment, by consulting Albutt [12] and Osler,[13] that the symptoms are identical. The evidences of anemia, weakness, breathlessness, palpitation and often digestive and menstrual disorders are stressed in both cases. One can find no point of distinction.

The Green Color.—Absence of the traditional green color of chlorosis is stressed by modern writers in differentiating chlorosis from hypochromic anemia. One wonders, however, whether this green color ever had any real existence. Certainly the contemporary accounts of a generation ago make no claim as to its constancy. "It must be borne in mind, however, that in many patients undoubtedly chlorotic this sign (the green color) may not be marked" (Osler,[13] 1894). "Many of these patients bear in their features the classical sign of their malady, but not so all of them; not a few of them carry colour (chlorosis florida or rubra"—Albutt,[12] 1909). Certainly the "green color" does not appear to be a sufficiently substantial point on which to base a fundamental differentiation of diseases, and one must remember that the so-called lemon yellow color of pernicious anemia stressed in the textbooks for years has assumed a somewhat mythical character, and at any rate is not seen nowadays.

The Degree of Anemia.—Another alleged point of differentiation between hypochromic anemia and chlorosis lies in the claim that the degree of anemia is less marked in the latter. This statement is not, however, supported by the facts. Osler [13] referred to a case in Thayer's series in which the red blood count was 1,950,000 with 17.5 per cent hemoglobin. The average hemoglobin value in Thayer's sixty-three cases was 42.3 per cent, with an average red cell count of 4,090,000, and the fact of the matter, which is clearly brought out in the protocols in the literature, is that in both chlorosis and hypochromic anemia one may encounter slight, moderate or severe degrees of anemia. Furthermore, the morphology of the blood in chlorosis as described,

15. Witts, L. J.: Chlorosis in Males, Guy's Hosp. Rep. **10**:417, 1930.

for example, by Osler [13] is identical with the modern accounts of hypochromic anemia: "If a drop of fresh blood be examined, the pallor of the individual corpuscles is at once apparent. There may be many poikilocytes, by which we mean deformed red globules assuming the most curious flask-like, hammer-shaped, or pyriform appearance."

Gastric Secretion.—Witts and others insist on the gastric anacidity of hypochromic anemia as an essential point in the differentiation of this condition from chlorosis in which there is said to be an abundance of acid secretion in the stomach. I have already pointed out, however, that cases indistinguishable from hypochromic anemia but without anacidity not infrequently occur, and Witts,[14] under the heading of "Late Chlorosis," reported a series of eighteen such cases arbitrarily separated from the anacidity group on the basis of their gastric secretion. As to chlorosis in the older sense, whereas the statement is frequently made in textbooks that acid is present in abundance, actual data from individual cases are meager. The literature was reviewed by Arneth [16] who pointed out that various workers have found either abundant acid, a low acid content or anacidity. It appears, therefore, that with both hypochromic anemia and with chlorosis any type of gastric secretion may be found.

Response to Iron Preparations.—The response to iron preparations appears to be identical in both chlorosis and hypochromic anemia. "Chlorosis is one of the few diseases of which the physician is a therapeutic master. A few weeks' administration of iron, together with an improved hygienic condition, usually suffice to restore a ruddy glow to the most pallid cheek" (Osler). Figure 8 in Osler's [13] article, picturing the rise of blood in a case of chlorosis from 1,900,000 to 5,100,000 after three weeks of iron therapy, is practically identical with many of the charts from recent papers on hypochromic anemia.

COMMENT

The first point that emerges from the preceding analysis is the impossibility of differentiating "chlorosis" in the nineteenth century sense from the hypochromic anemia of modern writers. Neither age, sex, symptoms, gastric analysis, hematologic examination nor response to iron therapy offer any tangible criteria for separating the two conditions. The next question is whether either disorder represents a truly specific disease or whether the cases classed as chlorosis and hypochromic anemia do not rather constitute a syndrome without fixed characteristics. The evidence seems overwhelmingly in favor of the latter view. That the syndrome manifests itself predominantly in women

16. Arneth, J.: Parallel laufende Magensaft- und Blut-Untersuchungen bei der Chlorose, Deutsche med. Wchnschr. **32**:666, 1906.

during the period from puberty to menopause is an unquestioned fact, and it seems reasonable, therefore, to suppose that menstruation is an important contributory cause. Granted that certain people have an abnormally feeble power of regenerating blood (whether this defective power is inherent or precipitated by inadequate diet or by other means), such a tendency would obviously be unmasked by menstrual bleeding especially if excessive. Menstrual bleeding is doubtless not the only factor, and loss of blood from hemorrhoids and peptic ulcer has also been stressed in the literature on chlorosis. The small number of cases of anemia of this general type in men is, then, probably to be explained by the absence of periodic losses of blood such as occur in women. Gastric anacidity can be fitted into the picture by invoking the observations of Mettier and Minot [17] that iron is better absorbed or at least more effective when the gastroduodenal medium is acid. At any rate, the whole situation offers a fertile field for careful studies of iron metabolism and of blood regeneration, which will doubtless lead to an eventual solution of the problem.

CONCLUSIONS

1. Chlorosis and idiopathic hypochromic anemia cannot be differentiated into independent entities.

2. Neither is a specific disease, but the cases represent a syndrome with many variations.

3. The frequency of these types of anemia in women is probably conditioned by menstrual bleeding.

4. An analysis of the literature and case reports bearing on these points are presented.

17. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia, Am. J. M. Sc. **181**:25, 1931.

RELATION OF PAIN OF PEPTIC ULCER TO GASTRIC MOTILITY AND ACIDITY

JACOB MEYER, M.D.

DOROTHY FETTER, PH.D.
AND
ALFRED A. STRAUSS, M.D.
CHICAGO

The pain of peptic ulcer is usually ascribed to one of two causes: gastric acidity or gastric hunger contractions. Ginsburg, Tumpowsky and Hamburger [1] ascribed the pain of ulcer to the increased gastric tension and correlated the pain with gastric hunger contractions. Carlson [2] also showed that the pain in ulcer was synchronous with hunger contractions. Reynolds and McClure [3] examined patients fluoroscopically, and found no relation between the gastric contractions and the pain in ulcer. Ortmayer's [4] observations related the pain to gastric acidity. Palmer [5] studied the subject extensively and reported a definite relation of gastric acidity to pain in gastric and duodenal ulcer. He found that the injection of 0.5 per cent hydrochloric acid into the stomach in patients with active sensitive ulcer usually produced the characteristic pain. He later claimed this as a specific test for ulcer. In a small group of cases Palmer was able to show the relation of the pain to gastric hunger contraction. He concluded: "Hydrochloric acid is the normal stimulus to the pain-producing mechanism of sensitive peptic ulcers. Normal gastric peristalsis may be an adequate mechanical

From the Stomach Study Group, Julius Rosenwald Grant, Michael Reese Hospital, and the Department of Physiology, University of Chicago.

1. Ginsburg, H.; Tumpowsky, I., and Hamburger, W. W.: Contribution to the Physiology of the Stomach: XXXV. The Newer Interpretation of Gastric Pain in Chronic Ulcer, J. A. M. A. **67**:990 (Sept. 30) 1916.

2. Carlson, A. J.: Contribution to the Physiology of the Stomach: The Origin of Epigastric Pains in Cases of Gastric and Duodenal Ulcer, Am. J. Physiol. **45**:81 (Dec.) 1917.

3. Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomachs in the Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, Arch. Int. Med. **29**:1 (Jan.) 1922.

4. Ortmayer, Marie: Gastric Motor Activity in Patients with Peptic Ulcer, Arch. Int. Med. **35**:423 (April) 1925.

5. Palmer, Walter Lincoln: The Mechanism of Pain in Gastric and Duodenal Ulcers: I. Achlorhydria, Arch. Int. Med. **38**:603 (Nov.) 1926; II. The Production of Pain by Means of Chemical Irritants, ibid. **38**:694 (Dec.) 1926; III. The Rôle of Peristalsis and Spasm, ibid. **39**:109 (Jan.) 1927.

stimulus in very sensitive ulcers. Hydrochloric acid may sensitize both the sensory and motor gastric mechanisms." Previous observers [6] introduced various amounts of hydrochloric acid into the stomach, varying in strength from 0.5 to 2 per cent, but failed to produce pain in normal persons or in patients with ulcer. Hardt [7] reported that the distress of ulcer could be relieved by 0.3 per cent hydrochloric acid.

Hardy [8] used Palmer's test, applying it to persons suffering from epigastric pain regardless of the seat of the lesion. He reported a positive acid reaction in only 65 per cent of 155 cases of ulcer that he investigated. He also studied 73 patients in whom no local lesion was discovered. He reported a positive acid reaction in 45 per cent of these cases. His results show that the acid test is not specific for ulcer.

We studied epigastric pain in relation to gastric motility and gastric acidity in 22 patients: 12 of these had duodenal, and 2 gastric ulcer. Nine of this group were operated on. The diagnosis in all cases was made on the basis of history, symptoms, physical signs and positive roentgen observations. The 8 remaining cases consisted of 4 cases of disease of the gallbladder and chronic appendicitis and 3 cases in which the final diagnosis was neurasthenia. One patient was studied who had a typical history of ulcer, but roentgen examination showed no pathologic condition of the digestive tract, and a satisfactory diagnosis was never reached.

METHODS

The patients selected for study were placed on a general ward diet. On this diet, the pain of the patient continued as before he entered the hospital. The following tests were then made:

1. The acid test was performed according to Palmer's technic. This consists of preliminary aspiration of the contents of the stomach after a fast for at least twelve hours. Then 200 cc. of 0.5 per cent hydrochloric acid is introduced into the stomach. After half an hour, if the patient feels no pain, an additional 200 cc. of the acid is again introduced and the patient is observed for another half an hour. If he still feels no pain, the procedure is repeated a second time. If in the course of one and a half hours, with a total of 600 cc. of acid in the stomach, the patient feels no pain, the test is termed negative, but if at any time during the test the patient complains, the test is considered positive. We controlled our tests by repeating them with water instead of acid

6. Lowenthal: Berl. klin. Wchnschr. **29**:1188, 1892. Schmidt, J. E.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **19**:278, 1909. Hurst, A. F.: The Sensibility of the Digestive Tract, London, H. Frowde, 1911.

7. Hardt, L. L. J.: Pain in Active Pathologic Processes in Stomach or Duodenum, J. A. M. A. **70**:837 (March 23) 1918.

8. Hardy, J. L.: The Role of Hydrochloric Acid in the Causation of Gastric Pain, Lancet **1**:711, 1929.

in those patients who reacted positively to the acid. This eliminated the possibility of the production of pain by the accumulation of a volume of fluid in the stomach.

2. In cases of duodenal ulcer a further test was performed by injecting acid directly into the duodenum; 50 cc. of 0.5 per cent hydrochloric acid was slowly injected and a period of ten minutes allowed to elapse. If no pain developed, the test was performed a second time, and if the patient was still comfortable a third test was tried. In cases in which pain developed, the experiment was repeated with water instead of acid.

3. The third type of experiment was done in order to study the effect of both gastric motility and gastric acidity on the production of pain. After fasting from twelve to eighteen hours, the patient swallowed two tubes: a Rehfuss tube through which fluid could be withdrawn and injected into the stomach, and a tube with a condon balloon attached so that a record of gastric motility could be obtained according to the method suggested by Boldyreff and perfected by Carlson. The gastric contractions were recorded, and then the effect of withdrawing gastric juice or introducing acid or water was studied. In cases of duodenal ulcer this procedure was repeated whenever possible with the tube in the duodenum. This proved difficult, as inflation of the balloon in the duodenum produced nausea, causing its regurgitation into the stomach. However, the relation of gastric contractions to duodenal contraction has been studied by Ivy and Vloedman [9] and by Quigley and Solomon.[10] This type of experiment was repeated as often as the endurance of the patient permitted.

In interpreting the records obtained, the temperament and emotional state of the patient must be considered. Such emotions as fear or rage tend to inhibit gastric contractions (Carlson [11]). The more phlegmatic type of patient showed considerable gastric motility the first time the tube was swallowed, while the excitable patient showed no motility whatever. Usually after a few trials the patient lost his fear of the tube and motility ensued. In some cases the patient objected so strenuously to swallowing the tube that the test could not be repeated. In this type of case, the patient's reaction to acid could be studied, but no conclusion could be reached as to the relation of motility to ulcer pain.

9. Ivy, A. C., and Vloedman, D. A.: The Small Intestine in Hunger, Am. J. Physiol. **72**:99 (March) 1925.

10. Quigley, J. P., and Solomon, E. I.: Action of Insulin on the Motility of the Digestive Tract: Action on the Human Duodenum; Action on the Colon of Dogs, Am. J. Physiol. **91**:488 (Jan.) 1930.

11. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916, p. 151.

RESULTS

In considering our results, those obtained in cases of ulcer will be taken first.

The patients were found to fall into two classes: (1) those who had pain response to an acid stimulus but showed no pain in relation to gastric motility and (2) those who had no pain response to an acid stimulus but had pain during periods of gastric motility. One of each of these types will be considered in detail, and the results in all cases tabulated.

TYPICAL CASES

CASE 1.—A man, aged 37, entered the hospital on March 31, 1931, with a complaint of epigastric pain coming on from about one to one and a half hours after meals and also after midnight; it was relieved by soda or food. Sometimes after he ate fried or highly seasoned foods, the pain came on immediately after meals, to be followed within from a half to three quarters of an hour by vomiting. Relief followed vomiting. These symptoms had been present for about ten years.

The Ewald meal showed a free acidity of 61 and a total acidity of 76. Fluoroscopic examination and roentgenograms demonstrated a definite ulcerous defect of the lesser curvature of the stomach. The diagnosis was later confirmed by operation.

The patient was put on a full ward diet and his symptoms were watched. On April 4 the acid test was performed according to Palmer's method.

Acid Test.—Preliminary aspiration yielded 5.5 cc. of gastric juice, alkaline and bile stained. Then 200 cc. of 0.5 per cent hydrochloric acid was introduced. Pain followed in five minutes, but was relieved by aspiration. The test was repeated with 200 cc. of water; no pain resulted.

Motility Test.—On April 8 preliminary aspiration yielded 30 cc. of gastric juice with a free acidity of 0 and a total acidity of 2. The motility test gave negative results, but pain was present. Then 140 cc. of fluid was aspirated showing a free acidity of 25 and a total acidity of 30. There was relief of pain on aspiration. One hundred and forty cubic centimeters of water was introduced; no pain was felt. The fluid was withdrawn in half an hour, and 140 cc. of 0.5 per cent hydrochloric acid was introduced. Pain occurred in five minutes; this was relieved by aspiration.

Third Test: Motility and Acidity.—On April 10 preliminary aspiration yielded 85 cc. of alkaline juice. A study of contractions showed slow changes in tone but no contractions when pain came on and aspiration was performed. Free acidity was 25; total acidity, 35. Relief from pain followed, and when the patient had been free from pain for forty minutes, another sample of gastric juice was taken revealing a free acidity of 15 and a total acidity of 25. Another pain period occurred later. Fifty cubic centimeters of gastric juice was aspirated, showing a free acidity of 30 and a total acidity of 45; relief from pain followed aspiration. A painless period then ensued, and 80 cc. of 0.5 per cent hydrochloric acid was introduced, followed immediately by pain; aspiration was again performed, but no relief was obtained until sodium bicarbonate, 30 grains (1.9 Gm.) was given.

In this case the pain seemed to depend on the acidity of the gastric content. All aspirations done during periods free from pain withdrew

gastric juice of low acidity, whereas all of those done during periods of pain withdrew a fluid with an acidity of 20 or over. The injections of acid always brought on severe pain. The pain showed no relation to the recorded gastric contractions.

In 8 of 15 patients with ulcer, pain occurred in response to the injection of hydrochloric acid and had no relation to the gastric motility.

Case 2.—Mrs. F., aged 29, was admitted to the hospital on March 3, 1931. She complained that for the last three years she had had attacks of pain lasting five days and occurring every three weeks. The pain was described as sharp, located in the umbilical region and radiating from there along the left costal margin to the axillary region. It came on about an hour after meals and at night, and was relieved by soda or milk and cream. For the last six weeks the pain had been present constantly and the patient frequently vomited, shortly after meals. Fluoroscopic examination revealed a large duodenal ulcer and the diagnosis was later confirmed by operation.

Table 1.—*Results in Cases Showing Pain in Response to an Acid Stimulus*

		Acid Test		Motility Test		
Case	Type of Ulcer	Number Positive	Number Negat've	Number Positive	Number Negative	Diagnosis Confirmed by
1	Gastric	3	..	..	2	Roentgenogram and operation
2	Duodenal	1	..	..	1	Roentgenogram and operation
3	Duodenal	3	..	..	1	Roentgenogram and operation
4	Duodenal	3	..	..	..	Roentgenogram and operation
5	Duodenal	3	..	..	1	Roentgenogram
6	Duodenal	4	..	..	2	Roentgenogram
7	Duodenal	3	..	..	2	Roentgenogram and operation
8	Duodenal	3	..	..	2	Roentgenogram and operation

The patient was put on a soft diet, on which her symptoms continued:

Acid Test.—On preliminary aspiration 200 cc. of gastric juice with a free acidity of 25 and a total acidity of 35 was withdrawn. Then 200 cc. of 0.5 per cent hydrochloric acid was introduced; no pain was noted after one-half hour. Again 200 cc. of 0.5 per cent hydrochloric acid was introduced; no pain occurred after one-half hour. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid was again introduced; after one-half hour no pain was felt. The patient was restless and tired.

Acid Test.—On March 14, preliminary aspiration yielded 100 cc. of gastric juice with a free acidity of 35 and a total acidity of 45. A Rehfuss tube was inserted into the duodenum. Then 50 cc. of 0.5 per cent hydrochloric acid was injected slowly; after ten minutes no pain was felt. Fifty cubic centimeters was again injected, and after ten minutes no pain was noted. Again 50 cc. was injected and no pain was felt. The patient stated that she had not experienced pain at any time.

On March 17, during a period of pain, the gastric motility was studied. Because of the patient's disinclination to swallow two tubes, only one with the balloon attached was given her; therefore, no study of gastric acidity could be made. The record showed vigorous type I contractions (Carlson[12]), which occurred at intervals of about a minute. During every contraction the patient registered pain.

12. Carlson (footnote 11, p. 44).

Our experiments on this patient then showed no pain in relation to gastric acidity, but indicated that the pain depended on gastric motility, since it occurred simultaneously with each contraction of the stomach.

In 6 of the other patients with ulcer, pain occurred synchronously with gastric contractions and not in response to acid stimulation.

One case of ulcer confirmed by operation could not be classified in either group.

CASE 3.—A man, aged 60, entered the hospital in July, 1930, complaining of epigastric pain coming on from two to four hours after meals, relieved by taking soda or food. Roentgenograms revealed a duodenal ulcer, and this diagnosis was later confirmed by operation. The patient was put on a milk and cream diet, but his pain continued.

On July 15, the acid test according to Palmer's technic was tried. Pain came on when the patient had 400 cc. of acid in the stomach, one hour after the test was started. This is a positive response. Two attempts were made to study the gastric motility but were unsuccessful because, in spite of starvation for fourteen

TABLE 2.—*Results in Cases Showing Pain During Periods of Gastric Motility*

Case	Type of Ulcer	Acid Test		Motility Test		Diagnosis Confirmed by
		Number Positive	Number Negative	Number Positive	Number Negative	
1	Duodenal	..	2	1	..	Roentgenogram and operation
2	Duodenal	..	5	3	..	Roentgenogram
3	Gastric	..	3	2	..	Roentgenogram and operation
4	Duodenal	..	3	3	..	Roentgenogram
5	Duodenal	..	2	2	..	Roentgenogram and operation
6	Duodenal	..	4	2	..	Roentgenogram

hours, hunger contractions of the stomach were completely absent. Nevertheless, the patient registered pain intermittently during the test. Aspiration during pain withdrew gastric juice ranging in free acidity from 15 to 19, with a total acidity always of about 30. Relief never followed aspiration. The introduction of from 200 to 400 cc. of 0.5 per cent hydrochloric acid in no way changed the character of the pain.

The studies on this patient indicate that his pain was not related to motility. However, the tube was in the stomach and the ulcer in the duodenum. A partial obstruction of the pylorus made it impossible to pass the tube into the duodenum, so we cannot be certain that duodenal contractions were not occurring while the test was done. Studies on the relationship of gastric and duodenal motility, however, show that the contractions occur nearly together, so that one would scarcely expect constant spasms of the duodenum while the stomach remained relaxed for a period of two hours.

Nor could the acid test be considered positive. Once, to be sure, it acted positively, but the patient volunteered the information that the pain, which was long delayed, was very slight. In cases in which the response to acid is late and is slight, one doubts the value of the acid

test. Presumably, a spontaneous pain might occur at such a time. We have records that show that the inhibitory effect of the introduction of acid on the gastric contraction disappears within half an hour, so that a late pain response to acid might in reality be due to motility.

In this case our studies show no relation between the pain of ulcer and either gastric motility or acidity.

The case of a man who showed no lesion of the stomach or duodenum should be recorded because he reported two types of pain, one of which we related to gastric contractions and the other to high gastric acidity.

CASE 4.—This patient complained of hunger pain occurring after a long period without food. Another kind of pain described as sharp and knifelike and located in the epigastrium occurred within an hour after eating. The symptoms had been present for ten years. The patient had lost 12 pounds (5.4 Kg.) within the last year. Fluoroscopic examination revealed no pathologic condition, and as an operation was not resorted to, the possible diagnosis of ulcer was uncertain.

Palmer's acid test was first tried. In a preliminary aspiration 12 cc. of fluid was withdrawn with a free acidity of 10 and a total acidity of 25. Then 200 cc. of 0.5 per cent hydrochloric acid was injected. Within five minutes a sharp and knifelike pain came on, similar to the type of pain that the patient experienced after eating. This pain was relieved by the administration of 25 grains (1.6 Gm.) of sodium bicarbonate.

A few days later, after a fasting period of twenty-four hours, the gastric motility was studied. The patient was complaining of hunger pain at the time that the record was taken. The gastric contractions were vigorous at first, and the patient registered pain simultaneously with each contraction or whenever the tonus was high. A quiescent period came on, and the pain ceased. At this time 100 cc. of hydrochloric acid was introduced. In five minutes the patient registered pain, which he described as the sharp epigastric pain that he usually felt after meals. He continued to register pain until 75 cc. of fluid had been withdrawn from the stomach; 100 cc. of water was then injected into the stomach. No pain followed.

In all except one of our definite cases of ulcer pain has occurred either with gastric contractions or with high gastric acidity. Case 4 is interesting as it shows that in certain persons pain can accompany both conditions. Since no definite diagnosis was made, no conclusions can be drawn. The man may have had neurasthenia and been more sensitive than the normal to visceral conditions.

In 9 cases of epigastric pain with no demonstrable lesion of the stomach or duodenum, 6 of the patients reacted positively to the acid test. Pain did not occur synchronously with gastric contractions in any of these cases.

DIRECT APPLICATION OF ACID TO ULCER

Hydrochloric acid, in dilutions of 0.5 per cent, 1 per cent and 5 per cent, was applied directly to the ulcer in 4 patients with gastric and duodenal ulcer during operation under local anesthesia. No pain

response was elicited. The patients, however, responded with pain when the mesentery was pulled or when an unanesthetized area of the skin was pinched. Two of these patients gave positive results for acid in the Palmer test, and 2 gave definitely positive reactions to the motility test.

COMMENT

The striking division of our cases into those showing a positive pain response to acid but a negative motility response and into a second group showing a positive motility but a negative acid response is somewhat difficult to explain in view of some of the previous observations on the mechanism of pain in ulcer. Palmer and others have emphasized the importance of acid in the production of pain. He spoke of the condition necessary for the positive reaction to acid as "a sensi-

TABLE 3.—*Results in Cases of Epigastric Pain Without Demonstrable Gastric or Duodenal Lesions*

Case	Condition	Acid Test		Motility Test	
		Number Positive	Number Negative	Number Positive	Number Negative
1	Disease of gallbladder	..	1	..	..
2	Disease of gallbladder	1	1	..	1
3	Disease of gallbladder	2	1	..	2
4	Disease of gallbladder	2	..	..	1
5	Chronic appendicitis	1	1	..	1
6	Neurasthenia	5	..	..	3
7	Neurasthenia	..	2	..	..
8	Neurasthenia	..	1	..	..
9	Neurasthenia	2	..	2	..

tivity of the pain-producing mechanism." He did not, however, define the factors of this pain sensitivity. He indicated that the quantity and the degree of acidity are important. Our observations on the direct application of acid to the ulcer would indicate that acid is not per se the important factor. Nor can increased general susceptibility to pain be a factor, for one of us has observed that patients with peptic ulcer, when subjected to tests for pain, respond in a normal or subnormal manner and are not hypersensitive. Konjetzny,[13] Faber[14] and others have called attention to the pyloric gastritis in gastric and duodenal ulcer. This gastritis occurs in the duodenum as well as in the antral portion of the stomach. The "sensitivity" to acid, using the expression of Palmer, we believe is due to the associated gastritis. This also offers a reasonable explanation for the recurrent periodic attacks of pain. Clinical observation recognizes the occurrence of gastritis of varying degree in cholecystitis and appendicitis. The positive acid response in

13. Konjetzny, G. E.: Beitr. z. path. Anat. u. z. allg. Path. **71**:595, 1923.

14. Faber, K.: Chronic Gastritis in Relation to Asphyxia and Ulcer, Lancet **2**:901, 1927

these cases can readily be explained on the basis of sensitivity to acid because of the gastritis. The failure to obtain hunger contraction in these conditions is readily explained by the lack of tonus and contractions that invariably accompanies varying degrees of gastritis.

How shall we explain the group of gastric and duodenal ulcers that do not give a positive response to acid but are positive for gastric hunger contractions? One possibility is that mechanical obstruction, due to relative duodenal stenosis or duodenal narrowing, may intensify the hunger contractions. Although many of the cases at operation revealed varying degrees of duodenal narrowing with scar formation, it does not seem to us that this offers an explanation of pain synchronous with hunger contractions in all cases. Carlson has called attention to the fact that there are persons who respond definitely with painful sensations to normal hunger contractions, independent of any organic lesion in the stomach. These persons may be considered hypersensitive to the gastric motor mechanism. Is it not conceivable that in ulcer a similar condition may exist? We are still at a loss to explain the negative response to acid. Our observations on the stomach and duodenum of these patients also reveal a moderate degree of gastritis. It is conceivable that the sensitivity to acid is dependent on the varying degree of gastritis and that in the absence of this gastritis the dominating factor is not the acidity but gastric motility?

According to Hurst,[15] the only stimulus that causes any sensation in the stomach and intestine is tension—"slight tension, the sense of fullness, greater tension the sense of pain." He advocates the view that "acid acts indirectly by giving rise to a protective reflex, which results in achalasia of the pyloric sphincter. . . . Achalasia and spasm of the pyloric sphincter only cause pain indirectly by preventing the relief of this tension in the pyloric vestibule, which the normal opening of the sphincter and the passage of chyme through the pyloric canal into the duodenum causes on the approach of each peristaltic wave." Our conception of the manner in which gastric motility produces pain in gastric and duodenal ulcer is one that is intimately associated with changes in the blood supply in and about the ulcerous area. Increased gastric contractions and gastric peristalsis we think are associated with depletion of the vascular bed in and about the ulcerous area, producing ischemia, asphyxia and resulting pain. In a previous communication (Meyer and Kartoon[16]) we advanced this hypothesis and suggested that the relief of pain on the intake of food, soda or spirits is intimately associated with improvement in the circulation of the stomach and

15. Hurst, Arthur F., and Stewart, Matthew J.: Gastric and Duodenal Ulcer, London, Oxford University Press, 1929, p. 159.

16. Meyer, Jacob, and Kartoon, Louis B.: Effect of Intravenous Injection of Foreign Protein on Peptic Ulcer, Arch. Int. Med. **46**:768 (Nov.) 1930.

local vascular improvement about the ulcerous area. Increased peristalsis in hunger or at the end of a meal results in a depletion of the vascular bed in and about the ulcerous area, with resulting asphyxia, edema and pain. This hypothesis offers a reasonable explanation of the rhythmical character of the pain in ulcer which is entirely independent of acidity. It may likewise be the explanation of the paradoxical fact that acid, such as hydrochloric, or some other irritant gives relief from pain in ulcer in some cases.

CONCLUSIONS

1. The results indicate that hydrochloric acid is not responsible for the pain in all cases of peptic ulcer.

2. As a result of experimental and clinical studies, we suggest that the pain in gastric ulcer is due to acid sensitivity when an associated gastritis is present. This same mechanism prevails in cholecystitis, appendicitis and probably colitis.

3. Pain in gastric and duodenal ulcer may be due to gastric hunger contractions and gastric motility.

4. The mechanism by which pain is produced by the hunger contractions and motility we believe is a depletion of the vascular bed in and about the ulcerous area resulting in asphyxia, edema and pain.

5. The positive acid response in cases without intrinsic gastric and duodenal lesions, as in disease of the gallbladder, chronic appendicitis and gastric neurosis, would indicate the unreliability of "the acid test" for gastric and duodenal ulcer.

Book Reviews

The Action of Muscles Including Muscle Rest and Muscle Re-Education. By Sir Colin Mackenzie, M.D., F.R.C.S., F.R.S. (Edin.), Professor of Comparative Anatomy and Director of the Australian Institute of Anatomy, Canberra; formerly member of the Council of the Anatomical Society of Great Britain and Ireland, and of the Staff of the Military Orthopaedic Hospital, Shepherd's Bush, London, and Examiner in Anatomy to the Universities of Melbourne and Adalaide; Co-Editor of "Treves' Surgical Anatomy." Second edition. Price, $3.50. Pp. 288, with 100 illustrations. New York: Paul B. Hoeber, Inc., 1930.

At the February meeting of the Congress on Medical Education, Medical Licensure and Hospitals, one session (on February 16) was devoted to physical therapy. This evidence of the increasing importance attached by the medical profession to this subject explains somewhat the demand for a second edition of this book, for, as Mackenzie says, physical therapy is myology, and it is only "a question of time when a Department of Myology will be a principal feature in every orthopedic institution." Muscles constitute more than 40 per cent of the weight of the ordinary man; treatment of their disabilities furnishes most of the work of the physical therapeutists, and a better understanding of their mode of action has already led to great improvement in treatment, in reeducation of muscles and in the after-lives of patients, especially of those disabled by poliomyelitis or wounds sustained at war. The results obtained by Mackenzie and others are so surprisingly good that study of the subject becomes an urgent obligation of the medical profession.

The first part of the book deals with general principles; the second and larger part, with particular muscles. Among the principles, some that are emphasized especially are:

1. The part actually played by a muscle is not easy to detect. It cannot be predicted *a priori*. It must be studied in action on the living body. The skill of palpating fingers is the only reliable guide.

2. Muscles act individually as units; one part cannot have an action opposing that of another part.

3. Each has an antagonist. Voluntary stimulation of a prime mover effects the relaxation of the antagonist. Such relaxation is a guide to determining the real function of prime movers. Judged by this criterion, the brachialis is the real flexor of the forearm and not the biceps, since stimulation of the brachial only is accompanied by relaxation of the triceps.

4. Absolute rest is essential in treatment. The notion that massage is necessary to preserve a muscle temporarily paralyzed is quite wrong.

5. The only real test for muscle recovery is scientifically directed volitional movement.

6. Muscles have several separate functions acquired serially in the course of evolution. The loss of function and its recovery follow in the patient the same order as did the development in evolution.

Whether one agrees with Mackenzie's statement of all these principles or not, the interest and therapeutic importance of them are obvious. The practical physician and nurse will be interested in comparing the statement of the actions of specific muscles with those made by other workers, especially with those of Miss Wright in this country. For the most part, they agree; sometimes, as in the case of the biceps brachii, they do not agree perfectly. In these instances, Miss Wright's statement seems to be in accord with the actual working of these muscles, as observed by the reviewer.

An especial feature of this book lies in the understanding and practical application of the evolutionary history of muscles, for they lose their actions and reacquire them in an order that is in strict accord with their progressive evolution. Few authors have ever brought to the consideration of muscle action in man so thorough an understanding of comparative anatomy and evolution.

The second edition contains a new section on the evolutionary rôle of muscles in the development and maintenance of the erect posture characteristic of man.

The book is both scientific and practical. It deals at an opportune time with an interesting and important subject. It cannot fail to be of great interest to all who seek to understand the action of muscles and to treat their disabilities. The application of some of the principles, not generally recognized, which are set forth clearly and convincingly, should result in saner treatment and much more complete restoration of function than has been expected hertofore even more than was thought possible by most workers.

Die Dickdarmschleimhaut, ihre normale und pathologische Funktion im Röntgenbilde. By Dr. Werner Knothe. Price, 8 marks. Pp. 53, with 113 illustrations. Leipzig: Georg Thieme, 1932.

In this monograph the author has attempted to show the value of the roentgenologic "relief picture" of the colonic mucosa.

The technic for the preparation of the patient for study of the colon is described. The bowel should be entirely empty. This is accomplished by giving enemas several times during the two days preceding the examination. As contrast material the author uses a mixture of three parts of barium sulphate prepared for x-ray work and seven parts of water. The contrast enema is given under fluoroscopic control with the patient in the prone position. The detail studies are made after the bowel has been emptied as completely as possible, the mucosa being covered with only a thin film of the contrast material.

After a short discussion of the anatomy and physiology of the normal colon, the roentgenographic appearance is described and illustrated. Three types are distinguished, namely, the quietly segmenting, the actively segmenting and the contracting. In all of these the folds of mucosa are quite uniform.

The greater portion of the first half of the monograph is devoted to manifestations of functional disturbances of the colon. In the author's opinion these findings are brought about through vagus irritation. They represent a state of spasm of the mucosa associated with a spasm of the muscularis propria. This leads to a disordered formation of folds even though there are no evidences of inflammation or other anatomic changes in the bowel. To prove this point he has studied the effect of cold enemas, pilocarpine and atropine on the colon. The first two definitely stimulated the bowel, throwing the mucosa into an increased number of irregular folds. Atropine relaxed the bowel after stimulation by cold or pilocarpine. These effects are illustrated.

The second half of the monograph deals with pathologico-anatomic changes of the colon. The development of nonspecific ulcerative colitis is divided into three stages each of which may be distinguished roentgenologically. The first or acute stage is characterized by broad areas of swelling, ulceration and undermining of the mucosa. In the second stage the ulceration and undermining disappear and the swelling subsides considerably. This suggests that healing is taking place, and in most cases the process does not extend beyond this stage. The characteristic of the third stage is its rather finely granular appearance without evidence of swelling. Very little is said about the roentgen findings in tuberculosis of the colon because the author states that this subject will be dealt with at another time. It is stated that appendical disease may result in cecal irritability. Diverticula of the colon produce irritation or partial obstruction only when secondary infection is present. No evidence of carcinomatous degeneration in diverticulosis was seen in the forty cases studied. Finally there is a short discus-

sion on changes in the relief picture by a neoplasm. Here also signs of irritability of the colon develop only after there is secondary infection of the lesion.

This monograph is highly recommended to those interested in diseases and disturbances of the colon. Its chief value lies in the numerous and exceptionally good illustrations. The text is primarily devoted to their explanation.

Herz und Angst. By Professor Ludwig Braun. Price, 6 marks. Pp. 119. Vienna: Franz Deuticke, 1932.

New points of view are likely to be stimulating and provocative. Such, indeed, describes the reviewer's reaction to the monograph of Professor Braun. The main line of argument relative to the important place that the symptom "Angst" takes in the clinical picture of cardiac disease is instructive and well repays the interest of the reader. The usual physical phenomena of cardiac disease are not emphasized. There are no description of pathology, little mention of standard methods of diagnosis and almost no mention of medical treatment. The monograph is devoted to the psychologic and emotional aspects of cardiac disease, especially as they are manifested in patients with the anginal syndrome. The discussion turns largely about the meaning of the word "Angst," its derivation, its development through various literatures and its significance to the physician at the bedside in the presence of the patient, whose outlook on life has been abruptly and fundamentally altered. Differing from fear in that it has nothing outside itself of which to be afraid, "Angst" appears where life is endangered as a "protective reaction in the lower, a conscious sensation in the higher organism." It is the constricting, tightening, crushing sensation, indescribable, unbearable and dreadful, which, once experienced, changes the entire emotional outlook of its victims. "The specific sensation of the heart, its psychic signature, its speech, is the "Angstempfindung."

This description of the emotional and psychologic status of the patient who has once endured the "Angst" of cardiac disease is calculated to widen the mental horizon of the practitioner, to give him a far better insight into the mind and character of the patient with angina than he has thought of before. On the other hand, the chapter on the "Diagnostic Significance of the Angsttraumes," so permeated with Freudian psychology, carries little conviction, especially to one unschooled in this system of psychology.

A final chapter on euthanasia is unrelated to the main theme of the book. As the title implies, this chapter is devoted to a discussion of a subject that may be academically plausible, but practically is far short of justifiable. Few are the physicians who wish to add to the power already possessed to relieve pain, the responsibility inevitably attendant on the right to end it.

Psychology and Psychiatry in Pediatrics: The Problem. Subcommittee on Psychology and Psychiatry, White House Conference on Child Health and Protection. Bronson Crothers, M.D., Chairman. Price, $1.50. Pp. 146. New York: Century Company, 1932.

The main thesis defended in this report is that adequate medical care of the child cannot be given without intelligent attention to any intellectual and emotional difficulties that may be present. Physicians are warned that unwillingness on their part to acquire the ability to deal wisely with problems involving the personality of the child may lead to transfer of this field to formal organizations or to persons without medical experience, which will diminish the prestige of the medical practitioner. There are extracts of discussions by Esther Loring Richards, Borden S. Veeder, Adolf Meyer, Douglas Thom and others. The workings of a typical child guidance institute are described in detail.

THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and as a medium of publication for research and observation in the domain of internal medicine.

Manuscripts for publication, books for review, and correspondence relating to the editorial management should be sent to the editor-in-chief, Dr. N. C. Gilbert, 535 North Dearborn Street, Chicago. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF INTERNAL MEDICINE. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones of illustrations will be supplied by the Association when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, published by the American Medical Association. This requires, in order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. A complete list of abbreviations for standard periodicals, together with a full discussion of the style of the A. M. A. publications, appears in The Art and Practice of Medical Writing, a comprehensive book on the preparation of medical manuscripts, published by the American Medical Association. Price, $1.50.

Matter appearing in the ARCHIVES OF INTERNAL MEDICINE is covered by copyright, but, as a rule, no objection will be made to its reproduction in reputable medical journals, if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the ARCHIVES OF INTERNAL MEDICINE, or in any of the other publications issued by the Association, will not be permitted.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The ARCHIVES OF INTERNAL MEDICINE is published monthly. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $6.00, including postage. Single copies, 75 cents, postpaid.

Checks, etc., should be made payable to the AMERICAN MEDICAL ASSOCIATION.

OTHER PERIODICAL PUBLICATIONS

of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (two volumes): Domestic, $7.00; Canadian, $8.50; foreign, $11.00. Single copies, 25 cents.

AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. It includes carefully prepared collective abstracts based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $9.50. Single copies, 85 cents.

ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $9.50. Single copies, 85 cents.

ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and full abstracts of the literature on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $9.00. Single copies, 85 cents.

ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $9.00. Single copies, 85 cents.

ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $7.00. Single copies, 75 cents.

ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original contributions in the field of pathology, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $7.00. Single copies, 75 cents.

ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $9.00. Single copies, 85 cents.

QUARTERLY CUMULATIVE INDEX MEDICUS—Quarterly. A complete subject and author index to the worth-while current medical literature of the world. Issued four times a year. Second and fourth volumes bound for permanent reference. Subscription price, calendar year: Domestic, $12.00; Canadian, $13.50; foreign, $13.50.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn St. CHICAGO

CONTENTS

PAGE

Pericarditis. Harry L. Smith, M.D., and Fredrick A. Willius, M.D., Rochester, Minn.:

I. Chronic Adherent Pericarditis 171

II. Calcification of Pericardium 184

III. Pericarditis with Effusion 192

Cholesterol of the Blood Plasma in Hepatic and Biliary Diseases. Emanuel Z. Epstein, M.D., New York 203

Anemia Associated with Biliary Fistula. S. V. Balderston, M.D., Evanston, Ill 223

Carbohydrate Metabolism in a Case of Hemochromatosis. Richard P. Stetson, M.D., and John P. Peters, M.D., New Haven, Conn 226

Hemochromatosis and Purpura. Richard P. Stetson, M.D., and Henry W. Ferris, M.D., New Haven, Conn 232

Importance of Hepatomegaly and Splenomegaly in Differential Diagnosis. Moses Barron, M.D., and A. B. Litman, M.D., Minneapolis 240

Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes: III. Chloroform Poisoning. T. L. Althausen, M.D., San Francisco, and E. Thoenes, Dr.med., Leipzig, Germany 257

Treatment of Lobar Pneumonia with Carbon Dioxide and Oxygen: Report of Twenty-Seven Cases. J. Fletcher Hanson, M.D., and Abner W. Calhoun, M.D., Atlanta, Ga. 269

Quinine Derivatives and Specific Immune Serum in the Treatment of Pneumococcus Infection. Hobart A. Reimann, M.D., and Johannes K. Moen, M.D., Minneapolis 276

Resuscitation of the Stopped Heart by Intracardial Therapy: II. Experimental Use of an Artificial Pacemaker. Albert S. Hyman, M.D., New York 283

Fibromyoma of the Uterus, Cardiac Failure, Anemia and Edema: Report of a Case. H. Brandman, M.D., Chicago. 306

Hyperparathyroidism Without Parathyroid Tumor: Report of a Case Improved by Partial Parathyroidectomy. Lewis H. Hitzrot, M.D., and Bernard I. Comroe, M.D., Philadelphia 317

Relations Between Primary Hypochromic Anemia and Chlorosis. Arthur L. Bloomfield, M.D., San Francisco. 328

Relation of Pain of Peptic Ulcer to Gastric Motility and Acidity. Jacob Meyer, M.D.; Dorothy Fetter, Ph.D., and Alfred A. Strauss, M.D., Chicago 338

Book Reviews 348